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Volume 2

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ACADEMICIAN BORIS ALEKSANDROVICH KAZANSKII

(On the 70th anniversary of his birth)

G. Ya. Kondrat'eva and E. A. Mikhailova

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Boris Aleksandrovich Kazanskii was born in 1891 in the city of Odessa in the family of a professor of philosophy. In 1918 he completed his studies in the natural division of the physicomathematical faculty of Moscow University, where he specialized in chemistry. At the end of the course B. A. was retained in the University by Prof. N. D. Zelenskii and has been working there up to the present time. In 1935 B. A. Kazanskii received the university degree of Doctor of Chemical Sciences and the title of Professor. Starting with 1944 B. A. Kazanskii became deputy director of the petroleum chemistry staff, and from 1950 to 1960 he was its director. From 1935 to the present time B. A. Kazanskii has also worked in the laboratory of catalytic synthesis, which he established in the Institute of Organic Chemistry of the Academy of Sciences of the USSR. Since 1954 he has been director of the Institute. In 1943 B. A. Kazanskii was elected member-correspondent, and in 1946 an actual member of the Academy of Sciences of the USSR. An active organizer and participant in a number of chemical meetings, conferences, and congresses, B. A. Kazanskii is a member of the Bureau of the International Union of Pure and Applied Chemistry.

The main direction of the scientific work of B. A. Kazanskii has been synthesis and the investigation of the catalytic transformations of hydrocarbons. He has published about 300 communications, but in this brief article we shall discuss only the most basic results of B. A. Kazanskii's many years of investigation. His series of studies in the paraffin, olefin, aromatic and alicyclic series of hydrocarbons have joined these formerly discrete groups of compounds into a general system and have shown the routes and the conditions for their reciprocal transformations.

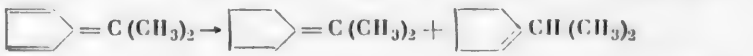
An important place among these transformations belongs to the unique dehydrogenation reaction of the paraffins, discovered by B. A. Kazanskii, in which aromatic hydrocarbons are formed – the so-called C-dehydrocyclization. This reaction is undergone by aliphatic hydrocarbons whose straight chain contains not less than six carbon atoms; the structure of the benzene homologs formed reflects the structure of the starting compound. Substituted cyclanes also may participate in the reaction. The phenomenon of C_6-dehydrocyclization was noted for the first time Kazanskii and Plate when they discovered ethyltoluene among the hydrogenolysis products of butylcyclopentane and explained its formation by the successively occurring processes of cyclization of the butylcyclopentane to hydroindane and hydrogenolysis of the latter [1]. When hexane and heptane are dehydrogenated, benzene and toluene are formed; dehydrocyclization of the higher paraffins proceeds with the formation of all the possible isomeric homologs of benzene. The mechanism of the reaction – the two-stage transformation of paraffin → alkylcyclohexane → alkylbenzene – was established by investigation of the aromatization of hydrocarbons with quaternary carbon atoms, the structure of which does not permit direct formation of aromatic compounds. Such paraffins, for example 3,3-dimethylhexane, under the conditions of catalytic cyclization are converted into a mixture of 1,1-dialkylcyclohexanes and aromatic hydrocarbons of lower molecular weight [3]. Platinized carbon [1,2,4] and other contact agents serve as catalysts for the aromatization. After a detailed study of a large number of oxide catalysts, carriers, and promoters B. A. Kazanskii and his coworkers obtained active samples of catalysts which gave significant yields (up to 50%) of aromatic hydrocarbons from synthol [a motor fuel] fractions C_7-C_{10} [5-8]. The aromatization reaction opens the possibility of the wide preparation of aromatic hydrocarbons from petroleum hexane and heptane. The yield of toluene from heptane on promoted potassium alumochromic catalyst [9] amounts to almost 70% at 515°, and at 550° the aromatization of n-hexane to benzene goes just as well.

On platinized carbon the cyclization of paraffins with closure of a five-membered ring – C_5-dehydrocyclization– also takes place. In this transformation paraffins with a straight chain of five carbon atoms take part, and also cyclic hydrocarbons with side chains. The capacity of hydrocarbons for C_5-dehydrocyclization is increased with an increase in their molecular weight and in the amount of branching of the chain. The reaction is catalyzed only by

The Editorial Board of the Journal of General Chemistry
warmly congratulates
Academician Boris Aleksandrovich Kazanskii
on the 70th anniversary of his birth
and wishes him many years of good health
and further fruitful scientific work.

platinized carbon, not by other metals of group VIII nor by the carrier of the platinum, activated carbon. The first example of the formation of cyclopentane hydrocarbons was the cyclization of n-hexane and n-octane, from which up to 10% of five-membered naphthenes were obtained at 310° [10]. It is most difficult to cyclize n-pentane [11] and easiest to cyclize the branched hydrocarbons where a greater spatial possibility of ring closure exists. Isooctane, for example, is converted to 1,1,3-trimethylcyclopentane in 25-32% yield [12], and 3-ethylpentane forms 12.5% of ethylcyclopentane [13]. 2,2,3- and 2,3,3-Trimethylpentanes in like manner give 1,1,2-trimethylcyclopentane [14]. Homologs of benzene and alkylcyclanes under these conditions form bicyclic hydrocarbons: propylbenzene is converted into indane, sec-butylbenzene into 2-methylindane, and isobutylbenzene into 3-methylindane [15]. Propylcyclopentane gives a small yield of cis-pentalane [16], which is also produced as a secondary reaction product when n-octane is dehydrocyclized [17]. The energy of activation of C_5-dehydrocyclization is 20 Cal/mole in the case of cyclization of the paraffins and about 27 Cal/mole for the cyclization of the alkylbenzenes [18].

B. A. Kazanskii has devoted much attention to the problems of hydrogenation of unsaturated hydrocarbons. Investigating the rules for catalytic addition of hydrogen to a double bond, he showed that the rate and the selectivity of the reaction is determined not only by the structure of the olefins, but also by the nature of the catalyst used. While the rate of absorption of hydrogen by the olefins RR'C = CHR" in the presence of platinum decreases when phenyl substituents are introduced into the molecule [19], yet in the presence of palladium and nickel the alkenylbenzenes are hydrogenated more rapidly than the aliphatic alkenes [20]. The relationship between the structure of the olefin and the nature of its hydrogenation has been shown in a series of substituted fulvenes: when diphenylfulvene is reduced with an insufficient amount of hydrogen, it quickly and selectively adds the hydrogen to the double bonds of the ring [21], while dimethylfulvene is hydrogenated unselectively and forms mixed reaction products [22].



Investigation of the catalytic hydrogenation of a conjugated system of double bonds has shown that in this case also the order of addition of the hydrogen depends on the structure of the starting diene and the catalyst used. As a rule, 1,2- and 3,4-addition of the hydrogen predominates and hydrogenation in the 1,4-position is more weakly expressed, especially in the dienes in which the substituents are on the terminal atoms of the conjugated system. These rules appear distinctly only in reduction over platinum; palladium and nickel catalysts cause isomerization of the unsaturated hydrocarbons and the composition of the reaction products formed is determined to a considerable extent by their equilibrium relationships. Isomerization of the olefins and dienes in the presence of palladium has been confirmed by an investigation of the catalysates from incomplete hydrogenation of the isomeric 2-methylpentenes [23] and hexadiene-1,5, from which in the presence of palladium, a mixture of hexene-1, hexene-2, and hexadiene-1,4 was obtained [24].

Some other rules were found for the reduction of unsaturated compounds with nascent hydrogen. It was determined that hydrogen which is produced by the decomposition of calcium, strontium, barium, and lithium ammoniate [25] hydrogenates two double bonds of the benzene ring and in this way converts the homologs of benzene into compounds of the cyclohexene series. Bicyclic aromatic systems and alkenylbenzenes (for example allylbenzene or isopropenylbenzene) are reduced in a similar manner. The position of the double bond in the side chain is not important since in the presence of a strong isomerizing agent – calcium amide – all the multiple bonds migrate [26].

Conjugated aliphatic dienes – 2,3-dimethylbutadiene-1,3– and dienes with separate double bonds, for example 2,5-dimethylhexadiene-1,5, also are reduced by the ammoniate. The addition of hydrogen goes predominantly, but not exclusively, in the 1,4-position; as in the cases of the other reducing systems also, hydrogenation is observed in the 1,2- and 3,4-positions [27]. The monoolefins also are reduced, less actively but still with appreciable speed, by nascent hydrogen [28]. The reduction reaction is ionic in character; it takes place in alkaline medium and its first stage is the addition to the C = C bond of two electrons and the second is the addition of protons.

$$>C{=}C< + 2\bar{e} \longrightarrow >C\bar{e}-C\bar{e}<; \quad >C\bar{e}-C\bar{e}< + 2H^+ \longrightarrow >CH-CH<$$

The formation of free hydrogen in this case ($H^+ + e \rightarrow H$; $2H \rightarrow H_2$) is an independent reaction, parallel to the reduction reaction. The proposed mechanism has been confirmed by measurement of the rate of reduction of olefins by potassium, sodium, and lithium in liquid ammonia in the presence of alcohols: the intensity of evolution of free hydrogen and the reducing capacity of these metals are in inverse relationship and the rate of reduction increases with a decrease in acidity of the alcohol [29].

A large group of publications by B. A. Kazanskii and coworkers relate to investigations in the field of hydrocarbons with small rings, the synthesis of these compounds, and the study of their contact transformations. The first direction [of investigation] concerns mainly synthesis in the cyclobutane series, where B. A. Kazanskii and his coworkers prepared a considerable part of the compounds that have been described. Many of the disubstituted cyclobutane hydrocarbons prepared were isolated as cis- and trans-stereoisomeric forms [30]. In the cyclopropane series of hydrocarbons we should mention the well worked out synthesis of 1,1,2-trimethylcyclopropane [31] and also the essential perfection of a method for preparing and purifying pharmacopeial cyclopropane, the best anesthetic agent for chest surgery [32], which very soon will be manufactured by the domestic industry.

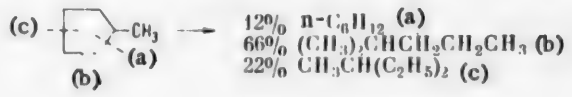
B. A. Kazanskii studied in detail the comparative stability and the transformation which C_3-C_4 cyclanes undergo under conditions of dehydrogenation catalysis. The hydrocarbons of the cyclopropane series in the presence of different catalysts easily add a molecule of hydrogen and are transformed into aliphatic compounds. The rules that determine the direction of rupture of the ring have been elucidated and it has been established that on most of the catalysts used, two independent processes proceed simultaneously— actual hydrogenolysis of the cyclopropane and its isomerization to an olefin with subsequent hydrogenation of this olefin [33-35]. If isomerization is excluded by proper selection of the catalyst, directed hydrogenolysis occurs and the "most readily hydrogenolyzed" C — C bond, distant from the substituent, is ruptured [31, 36]. When the cyclopropanes are isomerized, on the contrary, the "least readily hydrogenolyzed" bonds closest to the substituent are opened [35]: from methyldimethylcyclopropane there are produced 2,3-dimethylbutane, isohexane, and 2,2-dimethylbutane. Rearrangement of the three-membered carbon ring into an unsaturated chain takes place on silica gel at +2°, on aluminosilicate at about 50°, on kieselguhr at 120°, on pumice at 175°, and on carbon at about 200° [34]. If the double bond of a side chain is conjugated with the three-membered ring, the isomerization goes still more intensely. Alkenylcyclopropanes with a conjugated double bond are hydrogenated more easily than alkyl-substituted cyclopropanes. In the presence of palladium black, a specific catalyst of this reaction, vinyl- and isopropenylcyclopropanes add hydrogen first at the C — C bond of the ring; the product of the addition of two moles of hydrogen corresponds to the rupture of the least readily hydrogenolyzed bond. From vinylcyclopropane n-pentane is produced [37], from phenylcyclopropane, n-propylbenzene is obtained [38], and from methyl cyclopropyl ketone, pentanol-2 is formed [39].

The most interesting feature of the diphenylcyclopropanes proved to be the relationship of the conjugation of the phenyl and cyclopropyl rings to the steric factor. Conjugation of the phenyl and cyclopropyl radicals is developed to a considerable extent if the phenyl groups are in a spatially advantageous position. The cis-isomer of 1,2-diphenylcyclopropane, for example, according to Raman spectral data is less conjugated than the trans-compound [40], and 1,1-diphenylcyclopropane, where because of steric hindrances the phenyl rings are turned so that the axes of their π-clouds cannot be parallel to the axis of the π-cloud of the three-membered ring, reveals no conjugation at all in the Raman spectrum and does not add hydrogen under the usual conditions for hydrogenation of substituted cyclopropanes [41].

The cyclobutane system proved to be more stable under the conditions of dehydrogenation catalysis. When the stability of the three-, four-, and five-membered cyclanes are compared, it is found that under the conditions where the hydrocarbons with a three-membered ring are completely converted to paraffins (150-180°), the homologs of cyclobutane are unchanged; on the other hand they are almost entirely hydrogenated 250-260°, where cyclopentane only begins to add hydrogen [42]. A definite orientation is not observed in the addition of H_2 to the cyclobutane ring, and all four C — C bonds are equal in this reaction. The predominant formation of 2,3-dimethylpentane (70%) from isopropylcyclobutane is caused apparently by shielding of the bonds of the ring which are adjacent to the substituent [43]. Isomerization of the ring does not occur on hydrogenolysis; it is caused only by more active agents, for example aluminosilicate at a temperature above 200°. If a double bond is present along with the four-membered ring, the stability of the latter falls sharply; isopropenyl- and isopropylidenylcyclobutanes are isomerized on silica gel and kieselguhr as readily as the alkylcyclopropanes [44].

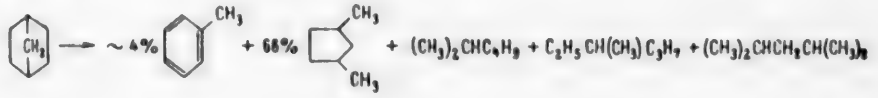
Hydrogenolysis of the cyclopentane hydrocarbons requires rather severe conditions: hydrogenation of unsubsituted cyclopentane in the presence of platinum on carbon begins at 250° and is almost quantitative (93.5%) at 275° [45]. Monoalkyl-, dialkyl-, and trialkyl-substituted cyclopentanes are hydrogenated with still more difficulty; the rate of the reaction decreases with the accumulation of a number of substituent groups and depends largely on their mutual arrangement. If we take the rate of hydrogenation of 1,2,3-trimethylcyclopentane as unity, then the rate of cleavage of cyclopentane, methylcyclopentane, 1,1-dimethylcyclopentane, 1,2-dimethylcyclopentane, and 1,3-dimethylcyclopentane can be arranged in the series ~ 46, ~ 28, ~ 30, ~ 8, ~ 4 [46,47]. The stability of the members

of the ring in the hydrogenation reaction is not the same: a substituent strengthens, so to speak, the C – C bond of the carbon atom where it is located; the weakest bond is that between secondary and tertiary carbon atoms [48].



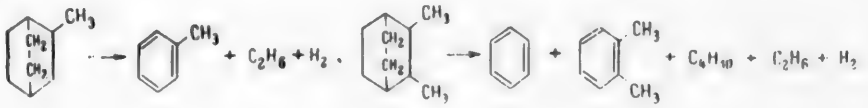
The rules found for the cleavage of five-membered rings are important for choosing a selective catalyst in the development of a method of analysis of gasolines.

An interesting example of the hydrogenolysis of a cyclopentane system was the cleavage of bicyclo(1, 1, 2) heptane, which at 300-310° (Pt contact) was converted to a mixture of toluene, 1,3-dimethylcyclopentane, and products of further hydrogenation of the latter [49].



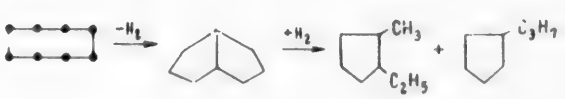
This reaction proved that bicycloheptane should be considered as a real five-membered ring and that the usual representation of it as a unique cyclohexane derivative does not correspond to the true nature of this compound. This conclusion also was confirmed by the spectral characteristics of bicycloheptane, where only the frequencies of a five-membered ring appear.

Hydrocarbons of the cyclohexane series differ from the five-membered naphthenes in their stability toward hydrogenolysis, although the cyclanes with a large ring size also can be hydrogenated to the corresponding paraffins [50-52]. In the absence of hydrogen, platinized carbon causes a number of other changes in the C_6-C_{10} cyclanes – isomerization, aromatization, or specific dehydrogenation with transannular splitting out of hydrogen and formation of bicyclic systems. Dehydrogenation catalysis has been studied in the most detail in the cyclohexane series; the first studies in this series, carried out by B. A. Kazanskii with N. D. Zelinskii, related to so-called irreversible catalysis [53]. A special case of dehydrogenation of cyclohexanes was the conversion of gem-dialkyl-substituted compounds, which split off one of the alkyl groups at 320° and give alkylbenzenes. Mainly the smaller radical is lost, but also the radicals that are simpler in structure; besides alkylbenzene, toluene and a small amount of xylenes also are produced [54]. When 1,1-disubstituted dicyclohexanes with two adjacent quaternary carbon atoms are aromatized the bond between the two rings is broken; toluene is the main product from 1,1-dimethyldicyclohexyl, and ethylbenzene from 1,1-diethyldicyclohexyl [55]. Similar conversions also are undergone by derivatives of bicyclooctane, a system of two fused six-membered rings; in the presence of platinum they split out the internal bridge and are aromatized [56].



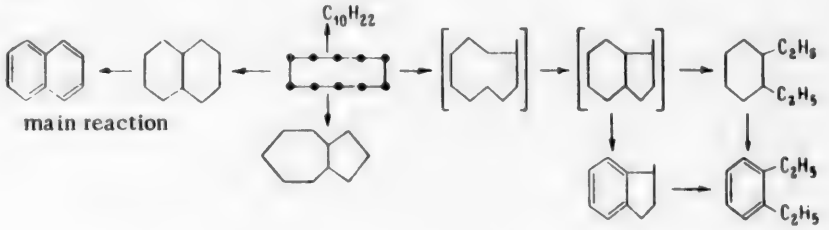
Alkylcycloheptanes on platinized carbon at 320° are converted to a mixture of isomeric methylalkylcyclohexanes which under these conditions are aromatized (the gem-substituted 1-methyl-1-alkylcyclohexanes which are formed are only partially aromatized [5,7]).

Starting with cyclooctane, the main direction of dehydrogenation becomes the transannular splitting out of and the formation of bicycloalkanes. Cyclooctane itself gives cis-pentalane [58], the yield of which on iron-platinum contact amounts to 75%.



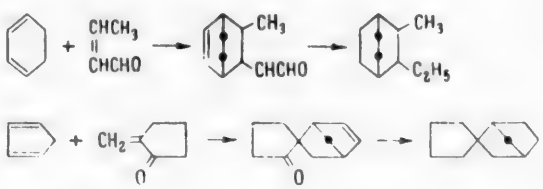
On other catalysts the direction of the reaction changes somewhat; thus, over nickel on kieselguhr at 200° there was observed, in addition to transannular C_5-dehydrocyclization, hydrogenolysis to n-octane and step-wise isomerization to alicyclic C_7, C_6, and C_5 hydrocarbons [50], and in the presence of aluminochromic contact agent ethylbenzene and xylenes were produced along with cis-pentalane. Transannular dehydrogenation of cyclononane over platinized carbon at 300° leads to the formation of indane and products of its hydrogenolysis – alkylbenzenes [51].

The transformations of cyclodecane are more complex. Besides the C_6-dehydrocyclization reaction with final formation of naphthalene and C_5-dehydrocyclization to cis-decahydroazulene, hydrogenation of cyclodecane and its isomerization to methylcyclononane take place on platinized carbon and the latter hydrocarbon naturally undergoes further cleavage [52]:



An important place is occupied in the investigations by B. A. Kazanskii and his coworkers by the synthesis of hydrocarbons of a high degree of purity. Many of these have been the objects of catalytic investigations, and a large number of pure standard hydrocarbons have been required as samples for compiling a spectral atlas [59]. A considerable portion of the compounds were synthesized for the first time; to prepare others it was necessary to refine and improve the known methods and to find new means of isolating and purifying them. Thus, in particular, a method was developed for the organozinc [60] and organomagnesium [61] synthesis of paraffins and alkenes with a quaternary carbon atom. Considerable success was achieved in the synthesis of substituted cycloalkanes. Of great importance was the improvement of the method for preparing cyclobutanedicarboxylic acid ester [62], which permitted increasing the yield of the final compounds by 1.5 – 2 times. A substantial contribution to the synthesis of cyclobutanes was a method of dehydration of dialkylcyclobutylcarbinols under conditions that exclude isomerization of the ring to a five-membered cycle [63]. A simple and original method of synthesis of isoalkylcyclopentanes from cyclopentadiene through the substituted fulvenes was developed [64].

Among the many alicyclic compounds synthesized were the difficulty obtainable gem-substituted dialkylcyclopentanes [65] and cyclohexanes [66] and the more complex bicyclic and tricyclic systems, for example [67]



Much attention has been given to the preparation of pure stereoisomeric forms of di- and trisubstituted cyclanes. Besides the cis- and trans-substituted cyclopropanes and cyclobutanes mentioned above, the individual cis- and trans-forms of 1,4-dimethyl-2-ethylcyclopentane [68], 1,2,3-trimethylcyclopentane [69], and a number of 1,2-disubstituted cyclohexanes [70-71] have been synthesized. The exact spectral characterization of a large number of the isomers prepared has permitted the drawing of a number of generalizations and establishing the basic principles of the optical identification of cis-1,2- and 1,4-dialkylcyclohexanes and the stereoisomeric trans-compounds [72]. Similar characteristics were established also for aromatic hydrocarbons with different numbers of radicals and types of substitution [73, 74].

B. A. Kazanskii has given much attention to new methods of investigation. Under his leadership highly effective fractionating columns, adsorption chromatography on silica gel, and dehydrogenation catalysis for selective dehydrogenation of the cyclohexane hydrocarbons were utilized for the first time in the Soviet Union, perfected, and introduced into practice in other laboratories: spectral methods of investigations were used, particularly Raman spectra. These analytical methods lay at the basis of the combined method [59] now used in many laboratories of the Soviet Union and some Peoples' Democracies for the study of the individual hydrocarbon composition of direct-distilled gasolines and cracking gasolines. Up to the present time the hydrocarbon composition of 36 direct-distillation gasolines from petroleums of Azerbaidzhan, Bashkiria, Kazakhstan, the RSFSR, Tataria, Turkmenia, Uzbekistan, and the Chinese People's Republic has been studied by this method [75]. After the introduction of a number of methodical changes and supplementary investigations in the field of the rules for the Raman spectra of hydrocarbons, the combined method was used for the establishment of the composition by narrow groups of ligroin-kerosene fractions [76] of direct distillation petroleum. For the investigation of the composition of catalysts for the dehydrogenation of isopentane and light fractions of cracking gasoline, B. A. Kazanskii and his coworkers successfully used gas-liquid chromatography methods [77]. The new methods of investigation permitted, on the basis of a knowledge of the detailed composition of the products of catalytic reactions, the discovery of the mechanism of chemical transformations.

Great skills, ability to penetrate to the essence of chemical processes, high accuracy and refinement of his experiments are distinguishing traits of B. A. Kazanskii, scientist. These he also requires and inculcates in his numerous students.

The scientific activity of B. A. Kazanskii has been highly valued by the Government. In 1945 he was rewarded with the order of the Red Banner of Labor and in 1953 with the order of Lenin. For his work in the field of catalytic transformations of hydrocarbons in 1949 B. A. Kazanskii received the Stalin prize of the first degree.

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THE EFFECT OF THE STRUCTURE OF COMPOUNDS ON THE KINETICS AND THE DIRECTION OF THEIR HYDROGENATION

I. THE ENERGY OF CONJUGATION AND THE KINETICS OF CATALYTIC HYDROGENATION OF BENZENE, PYRIDINE, AND PYRROLE

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The determination of the rules for the effect of energetic and geometric factors on the rate and direction of reaction is of basic interest for the theory and practice of catalysis. In connection with this it was expedient to carry out a study of the effect of the structure of compounds on the rate and direction of the catalytic hydrogenation reaction in such a way as to obtain information on the influence exerted by each of the effects elicited by the introduction of a substituent into the compound taken as a standard. Among these effects may be that of polarization, of conjugation (influence of the energy of conjugation and the energy of hyperconjugation), and steric effects. Such an approach may permit us to pass from a statement of these or other cases of the experimentally observed effect of the structure of a compound on the reaction rate to a consideration of the causes responsible for this effect. Suitable selection of the compounds can be made so that only one of the above-mentioned effects will prevail and the effect of the rest can be disregarded.

We first decided to study the effect exerted by the presence of energy of conjugation in a compound with aromatic or conjugated bonds on the kinetics and the direction of catalytic hydrogenation of these bonds. To elucidate this problem we carried out a systematic quantitative investigation of the hydrogenation of a considerable number of compounds with aromatic or conjugated bonds, comparing these compounds with respect to various criteria.

1st group. A study was made of compounds having a considerable energy of conjugation and differing in their chemical nature (benzene, pyridine, pyrrole, furan, thiophene, 1,1-diphenyl-2-picrylhydrazyl, ferrocene).

2nd group. Under comparable conditions we investigated the hydrogenation of compounds with large energies of conjugation in comparison with the hydrogenation of closely related compounds having small energies of conjugation or having no energy of conjugation (benzene, cyclohexadiene-1,3,cyclohexadiene-1,4, cyclohexene, furan, and dihydrofuran-3,4).

3rd group. A study was made of the kinetics of hydrogenation of compounds with small energies of conjugation in comparison with similar compounds having no energy of conjugation (cyclopentadiene and cyclopentene, cis- and trans-isoeugenols and eugenol, benzoic and phenylacetic acids, phenylcyclopropane and ethylcyclopropane, diphenyl and diphenylmethane).

4th group. An investigation also was made of the influence exerted on the rate of hydrogenation by the introduction of substituents causing the appearance of other effects than energy of conjugation (derivatives of benzene, pyrrole, pyridine, and furan).

In the present and the next communication data will be presented on the hydrogenation of compounds of the first group.

As is well known, the physical concept of energy of conjugation is that it transmits the energy of interaction of the π-electrons of the conjugated system of multiple bonds in the molecule. Since there are very few qualitative data on the influence of the energy of conjugation on the rate of hydrogenation, it was natural to consider first of all how the phenomenon of conjugation itself affects the rate of hydrogenation.

There are indications [1-6] that the conjugation of a double bond with a phenyl or carboxyl group lowers the rate of hydrogenation of the double bond in comparison with the corresponding unconjugated compounds. This rule, however, cannot be considered absolute, since under other conditions the introduction of a phenyl group in conjugation with a double bond increases the rate of hydrogenation [7-10].

Conjugation of a double bond with a carbonyl group as a rule leads to an increase in the rate of hydrogenation [1,2,11-14]. This conclusion is contrary to the opinion of Huckel [15] that an isolated double bond is hydrogenated more rapidly than one in a conjugated system of the type C = C − C = O. This conclusion of Huckel was drawn on the basis of studies [16, 17] in which hydrogenation of d-carvone was carried out with the formation of carvotan-acetone after addition of one mole ofhydrogen and further conversion of the latter compound to tetrahydrocarvone. From a consideration of references [16-19], however, it follows that in compounds of this type the determining factor is not conjugation, but the position of the double bond: a double bond in a side chain always is hydrogenated with greater rapidity.

On the basis of the data found in the literature it is difficult to draw definite conclusions with regard to the effect of conjugation on the hydrogenation of a system of conjugated bonds, since after the start of the reaction it is possible for a stable mixture of compounds to arise, which gives the process a very complex character. This problem will be considered in subsequent communications. It may be noted, however, that according to the data of Smith et al. [20] cyclohexadiene-1,3, which has a conjugated system, is hydrogenated on a platinum catalyst more rapidly than cyclohexadiene-1,4. According to the data of B. D. Polkovnikov [21] the rate of hydrogenation is higher for cyclopentadiene than for cyclopentene. On the other hand, Foresti [22] found that conjugation decreases the rate of hydrogenation of a double bond: cyclopentadiene, for example, was hydrogenated according to Foresti more slowly than cyclopentene.

The hydrogenation of aromatic bonds definitely proceeds at a lower rate than the hydrogenation of unconjugated double bonds [23, 24], although there are extremely few quantitative data [22, 20, 10].

With regard to the causes of the effect exerted by conjugation, the literature considers only the cases where a decrease in the rate of hydrogenation is associated with the conjugation. Most authors [25-31] associate the difficulty of hydrogenation of conjugated systems with their increased energetic stability, i.e., in the final analysis with the presence of energy of conjugation. Smith [20, 32, 33] came to some other conclusions in his studies, which were undertaken for the special purpose of investigating the effect of the energy of conjugation on the kinetics of catalytic hydrogenation. It was found that the energies of conjugation of the compounds studied did not enter into the experimentally determined energies of activation of hydrogenation. Hence it was concluded that the lower rate of hydrogenation, for example, of the benzene ring in comparison with the cyclohexadienes cannot be ascribed to the energy of conjugation of benzene, but is associated with some other factors. It was suggested that the energy of conjugation of a compound is completely lost upon adsorption of the compound on the surface of a catalyst and does not affect the kinetics of hydrogenation. The hypothesis of complete loss of the energy of conjugation by a compound when it is adsorbed on a catalyst also has been expressed in reference [28, 34]. A more likely view [35] is that upon catalytic adsorption a part of the energy of conjugation is lost.

EXPERIMENTAL

We carried out the study of the kinetics of hydrogenation in a glass vessel 180 mm in length and 35 mm in diameter at atmospheric pressure. A jacket was sealed onto the vessel for holding the temperature constant, which was accomplished with the aid of a TS-15 ultrathermostat. One of the outlets of the vessel was connected with a gas-measuring buret; in some experiments an automatic gasometer [36] was used in place of the buret. The high-speed shaker had a length of stroke of about 13 cm and made it possible to work at a shaking rate that provided for carrying out the reaction in the kinetic range. Actually the rate of hydrogenation of benzene on rhodium catalyst in acetic acid was practically unchanged if the number of oscillations was increased from 700 to 1100 per minute. This fact, that the external retardation of diffusion did not affect the rate of reaction, was also confirmed by the direct proportional relationship between the rate and the amount of catalyst. The appropriate data are presented below.

The electrolytic hydrogen used in the experiments was passed through a purifying system consisting of a column with silica gel and bottles with concentrated potassium hydroxide, a neutral solution of permanganate, and an alkaline solution of pyrogallol, and through quartz tubes, heated in furnaces, with palladinized asbestos and copper on kieselguhr.

The rate of hydrogenation was determined by the volume of hydrogen absorbed in 15, 30, and 60 seconds depending on the experimental conditions; the data obtained were converted to STP. For our study of the reaction we employed the potentiometric method first developed by D. B. Solok'skii [37]. A platinum electrode into the vessel was introduced and, close to it, a capillary filled with filter paper, agar-agar, and saturated potassium chloride solution. The capillary was connected through a flexible tube with a saturated calomel half-cell. The platinum electrode and the saturated calomel half-cell was connected with a PPTV-1 potentiometer. The EMF was measured by the compensation method. A saturated calomel half-cell was used as the comparison electrode. An SR apparatus with a sensitivity of 1 mm = $2 \cdot 10^{-9}$ a served as a null galvanometer.

The hydrogenation was carried out in the presence of a rhodium catalyst which was prepared by reduction of rhodium dichloride on activated aluminum oxide (catalyst No. 5 contained Rh equal to 1.2% by weight of the aluminum oxide).*

In carrying out the experiments we tried to avoid the effect of extraneous complicating factors in experiments that were compared. In each experiment (with the exception of special cases) a new portion of catalyst was used. We prepared amounts of catalyst necessary only for carrying out experiments on the hydrogenation of compounds to be compared. From time to time the activity of the catalysts was checked by measuring the rate of hydrogenation of benzene. Data on the kinetics of hydrogenation were compared only for compounds which were hydrogenated under identical conditions, namely on sample from the same lot of catalyst saturated for a given time, in one solvent subjected to standard purification, etc. This standardization enabled us to obtain good reproducibility of results. The potential of the catalyst was measured under conditions of intensive bombardment of the platinum electrode by particles of the catalyst and in the presence of a sufficient amount of catalyst to guarantee complete imposition of the potential of the catalyst on the platinum electrode.

Hydrogenation of benzene, pyridine, and pyrrole. All the compounds studied were subjected to preliminary purification. Benzene (c.p.) was treated with sulfuric acid and with sodium and was distilled; n_D^{20} 1.5019, d_4^{20} 0.8803. Pyridine was distilled, shaken with Raney nickel, dried, and again distilled; b.p. 80-80.5°, n_D^{20} 1.5094, d_4^{20} 0.9825. Pyrrole (Kahlbaum brand) was shaken with Raney nickel, dried with freshly calcined potassium hydroxide, and distilled in a current of nitrogen freed of traces of oxygen; b.p. 131-132°, n_D^{20} 1.5085. Furan (c.p.) was distilled several times, among them over sodium; b.p. 31-32° (748 mm), n_D^{20} 1.4218, d_4^{20} 0.9371.

In all the experiments 0.0018% alcoholic alkali was used as the solvent.

Benzene was hydrogenated with stoichiometric absorption of hydrogen to form cyclohexane (Table 1). The rate of hydrogenation was practically constant for almost the entire course of the reaction (Fig. 1). When the initial concentration C_0 of the benzene was changed [increased to 0.3701-0.2160 M and decreased to 0.0252 M from 0.1010-0.0875 M (Experiments 2,3,5,6)], the rate of the reaction was little changed. It therefore may be considered that the hydrogenation of benzene is of zero order. When the amount of catalyst was changed within the limits studied, the rate of hydrogenation of benzene was proportional to the amount of catalyst (Table 1, Experiments 11-14, Fig. 1). Measurement of the potential of the catalyst showed that benzene is hydrogenated at a potential equal to the reversible hydrogen potential (RHP). In a series of experiments the shift amounted to 5-6 mv, which is close to the RHP. With an increase in temperature the rate of hydrogenation of benzene at first increased, and then began to fall. This phenomenon has been observed by other authors also [38] and is associated, apparently, with a change in the limiting step of the process. The energy of activation for the temperature intervals 2-20° and 30-40° was 4.1 and 4.4 Cal** /mole, respectively (Fig. 2).

Pyridine also was hydrogenated to piperidine with the absorption of exactly 3 moles of hydrogen (Table 2). From Fig. 3 and Experiments 20-23 (Table 2) it follows that the hydrogenation of pyridine proceeds according to an equation of zero order. Actually, up to 80% conversion the rate of hydrogenation of pyridine remained practically constant; experiments with a change in concentration showed that when the concentration C_0 of pyridine was decreased from 0.1089 to 0.0272 M and when it was increased to 0.233 M, the rate of hydrogenation did not change. The rate of hydrogenation of pyridine was directly proportional to the amount of catalyst (Table 2, Experiments 20, 33, 34). When the pyridine was introduced, the potential of the rhodium catalyst immediately shifted in the cathode direction by 65-70 mv (Fig. 3); this shift continued to increase during hydrogenation, sharply at first and then more slowly.

* Detailed data on the preparation of the catalyst will be reported in a separate communication.

** Here used to denote kilocalories – Publisher.

TABLE 1. Hydrogenation of Benzene on Rhodium Catalyst

Expt. No.	Initial weight of benzene (in g)	Initial concentration (M)	Theoretical volume of hydrogen for complete hydrogenation (in ml)	Actual volume of hydrogen adsorbed (in ml)	Temperature of experiment	Amount of catalyst (in g)	Rate constant of hydrogenation for zero order (ml/min)
1	0.1083	0.0923	93.1	92.4	20°	1.0	3.8
2	0.1023	0.0875	88.3	88.0	20	1.0	4.1
3	0.4336	0.3701	372.1	370.9	20	1.0	3.7
4	0.1185	0.0505	101.0	101.0	20	1.0	4.1
5	0.1182	0.0252	101.0	100.1	20	1.0	3.9
6	0.1182	0.2160	101.0	99.7	20	1 0	4.2
7	0.1182	0.1010	101.0	100.7	40	1.0	2.4
8	0.1182	0.1010	101.0	100.3	30	1.0	2.9
9	0.1182	0.1010	101.0	100.4	10	1.0	3.3
10	0.1182	0.1010	101.0	100.6	2	1.0	2.6
11	0.1182	0.1010	101.0	100.9	20	1.0	4.0
12	0.1182	0.1010	101.0	100.5	20	1.0	3.5
13	0.1182	0.1010	101.0	100.7	20	2.0	8.1
14	0.1182	0.1010	101.0	99.8	20	0.5	2.1
15	0.1135	0.0971	97.5	97.1	40	1.0	2.3
16	0.1135	0.0971	97.5	97.0	30	1.0	2.7
17	0.1135	0.0971	97.5	97.2	10	1.0	3.0

TABLE 2. Hydrogenation of Pyridine on Rhodium Catalyst

Expt. No.	Initial wt. of pyridine (in g)	Initial conc. of pyridine (M)	Theoretical volume of H_2 required for hydrogenation of pyridine to piperidine (in ml)	Actual volume of hydrogen absorbed (in ml)	Temperature of experiment	Amount of catalyst No. 5 (in g)	Rate constant for zero order (ml/min)
18	0.1041	0.0440	88.5	88.8	20°	1.0	4.7
19	0.1129	0.0945	95.3	95.5	20	1.0	5.0
20	0.1292	0.1089	109.9	109.8	20	1.0	4.8
21	0.1292	0.0545	109.9	108.5	20	1.0	4.7
22	0.1292	0.0272	109.5	109.4	20	1.0	4.4
23	0.1292	0.2331	109.9	109.6	20	1.0	4.6
24	0.1292	0.1089	109.9	109.0	20	1.0	2.4
25	0.1292	0.1089	109.9	109.5	10	1.0	3.3
26	0.1292	0.1089	109.9	109.2	25	1.0	5.6
27	0.1292	0.1089	109.9	108.9	30	1.0	6.1
28	0.1292	0.1089	109.9	109.5	40	1.0	6.6
29	0.1292	0.1089	109.9	109.0	50	1.0	6.1
30	0.1292	0.1089	109.9	109.3	60	1.0	5.5
31	0.1077	0.0905	91.4	91.2	40	1.0	6.7
32	0.1077	0.0905	91.4	91.0	60	1.0	5.3
33	0.1287	0.1082	109.0	105.1	20	2.0	9.7
34	0.1287	0.1082	109.0	106.6	20	0.5	2.3

Such a shape of the potential curve is associated, apparently, with the reaction of an electron pair of the nitrogen atom in the rings of the pyridine and the piperidine produced with the surface of the catalyst. With an increase in temperature to 40° the rate of hydrogenation of pyridine increased (Table 2, Experiments 20, 24-28). With a further rise (at 50 and 60°) the rate decreased (Experiments 29, 30). The energy of activation was 6.3 Cal/mole for the temperature interval 2-25°. For the interval 40-60° the energy of activation was negative.

The hydrogenation of pyrrole proceeded to the formation of tetrahydropyrrole with stoichiometric absorption of 2 mole of hydrogen (Table 3) and conformed with the equation for zero order. Actually, a change in the initial concentration of the pyrrole within the interval 0.0278-0.2391 M slightly affected the rate constant of the hydrogenation reaction (Table 3, Experiments 36-39). The constancy of the rate up to 90% conversion (Fig. 4) also indicated the zero order of reaction. With an increase in the amount of catalyst, the rate of hydrogenation of pyrrole increased

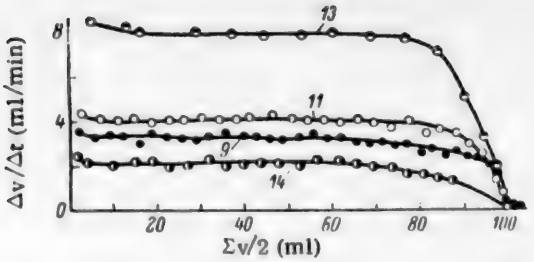

Fig. 1. Hydrogenation of benzene on rhodium. Concentration curves for the rate of reaction ($\Delta v/\Delta t$) vs. average concentration of benzene ($\Sigma v/2$). Numbers on curves correspond to experiment numbers in Table 1.

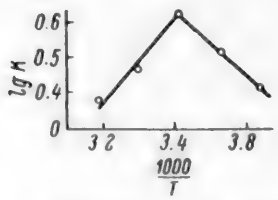

Fig. 2. Hydrogenation of benzene on rhodium. Temperature relationship of rate constant.

in direct proprotion to this amount (Experiments 36, 45, 46). Pyrrole, like pyridine, shifted the potential of the catalyst in the direction; this shift increased with an increase in the percent of conversion and toward the end of the reaction it amounted to 80 mv (Fig. 4). Evidently in this case also the shift in the potential of the catalyst in the cathode direction was associated with the reaction of the nitrogen atom of the pyrrole ring with the surface of the catalyst. An increase in the temperature over almost the whole interval investigated increased the rate of hydrogenation. Only above 50° did a decrease in the rate of hydrogenation start (Experiments 42,43). The energies of activation for the temperature intervals 10-30°; 30-50°; and 50-60° were equal to 7.0, 1.8, and 8.4 Cal/mole, respectively.

When benzene, pyridine, and pyrrole were hydrogenated, the reaction was carried out, as a rule, on catalysts saturated with hydrogen. In individual experiments the saturation of the catalysts was not carried out, and no essential change in the rate of the process and the nature of the kinetic curve was observed.

DISCUSSION OF RESULTS

The order of hydrogenation of all three of the compounds mentioned proved to be zero. Under comparable

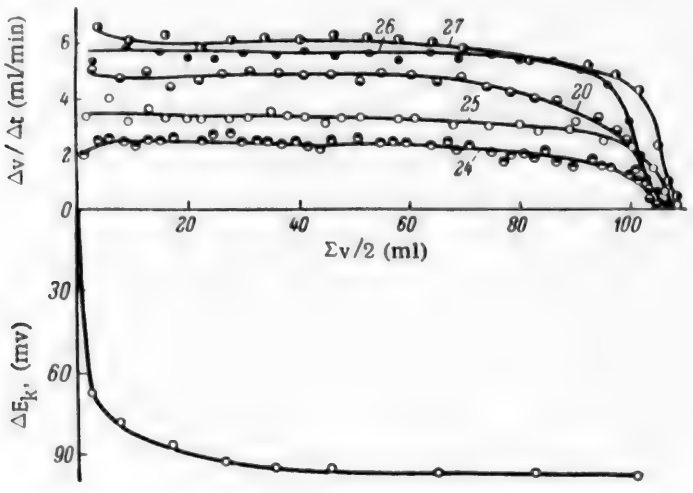

Fig. 3. Hydrogenation of pyridine on rhodium. Concentration curves above, potential curve below. Numbers on curves correspond to numbers of experiments in Table 2.

conditions (20°, 1 g of catalyst) the average rate constants obtained for the reaction were: for benzene 4.0, for pyridine 4.7, for pyrrole 4.9 ml/min. (Tables 1-3). The rate of reaction had a temperature maximum for these compounds as follows: for benzene approximately 25°; for pyridine approximately 40°; and for pyrrole approximately 45°. The existance of a temperature maximum for hydrogenation has been explained previously [38]. The energies of activation were found to be: for benzene 4.1 Cal/mole at 2-20° and 4.4 Cal/mole at 30-40°, for pyridine 6.3 Cal/mole at 2-25°, and for pyrrole 7.0 Cal/mole at 10-30° and 8.3 Cal/mole at 50-60°.

TABLE 3. Hydrogenation of Pyrrole on Rhodium Catalyst

Expt. No.	Initial amount of pyrrole (in g)	Initial concentration of pyrrole (in M)	Theoretical amount of hydrogen required for hydrogenation of pyrrole to tetrahydropyrrole (in ml)	Actual amount of hydrogen adsorbed (in ml)	Temperature of experiment	Amount of catalyst No. 5 (in g)	Rate constant of hydrogenation for zero order (ml/min)
35	0.1405	0.1394	93.6	93.4	20°	1.0	4.8
36	0.1120	0.1115	74.7	74.6	20	1.0	5.0
37	0.1120	0.0505	74.7	74.3	20	1.0	4.8
38	0.1120	0.2391	74.7	74.1	20	1.0	4.8
39	0.1120	0.0278	74.7	74.0	20	1.0	4.9
40	0.1120	0.1115	74.7	73.8	10	1.0	3.2
41	0.1120	0.1115	74.7	74.5	30	1.0	7.2
42	0.1120	0.1115	74.7	73.9	40	1.0	8.2
43	0.1120	0.1115	74.7	74.5	50	1.0	8.7
44	0.1120	0.1115	74.7	74.1	60	1.0	7.1
45	0.1120	0.1115	79.7	74.3	20	2.0	10.1
46	0.1120	0.1115	74.7	73.6	20	0.5	2.4
47	0.1405	0.1394	93.6	92.8	40	1.0	8.0

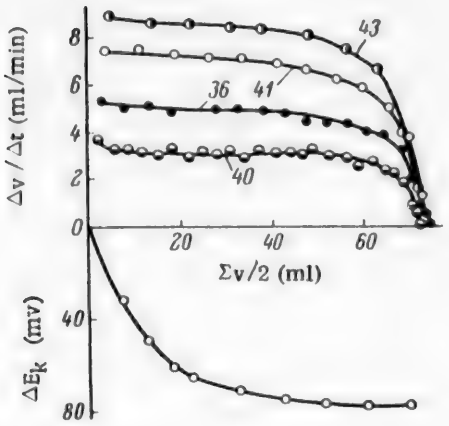

Fig. 4. Hydrogenation of pyrrole on rhodium. Concentration curves above, potential curve below. Numbers on curves correspond to numbers of experiments in Table 3.

The potential of the rhodium catalyst in hydrogenation corresponded almost exactly to the oxidation-reduction potential for benzene, was shifted by 70 mv in the cathode direction for pyridine, and was shifted by 80 mv in the same direction for pyrrole.

SUMMARY

The kinetics of the liquid-phase hydrogenation of benzene pyridine, and pyrrole has been studied for the first time in acetic acid solution on a rhodium catalyst and the potential of the latter has been determined at the time of the catalytic process.

The rate constants for the hydrogenation of benzene, pyridine, and pyrrole at 20° are arranged in increasing order. These compounds also are arranged in the same order with respect to the shift in potential of the catalyst in the cathode direction.

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FACTORS OF THE PARTIAL RATE OF EXCHANGE OF DEUTERIUM IN DIMETHYLANILINE WITH A SOLUTION OF POTASSAMIDE IN LIQUID AMMONIA AND THE MECHANISM OF BASIC DEUTERIUM EXCHANGE

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Determination of the factors of the partial rate of deuterium exchange between aromatic compounds and a solution of potassamide in liquid ammonia has made possible exposition of the role of the inductive effect in exchange reactions with a base and the statement of an idea concerning their mechanism. This proved to be analogous with the mechanism of metallization reactions of organoalkali compounds (reactions of the type of protophilic substitution) [1,2].

Setting ourselves the problem of additional grounds for the generalizations that had been made, we found it important to turn to compounds with substituents which usually are distinguished by the most clearly expressed electron-donor properties (amino and dimethylamino groups), since in this case the confirmation of rules for deuterium exchange which depend on the inductive shift of electrons in the direction of the nitrogen atom of the substituent would be especially convincing. Aniline was not suitable for the projected work because it reacts with potassamide, and we therefore settled upon dimethylaniline.

The study of deuterium exchange in dimethylaniline was of interest in yet another respect. It had been shown previously [3] that the hydrogen atoms in dimethylamino and methoxy groups connected with an aromatic ring participate in isotope exchange reactions of hydrogen which are catalyzed by potassamide. To determine the nature of the effect of an aromatic ring on the mobility of hydrogen atoms of a methyl group isolated by a hetero atom it was essential to accumulate data on the mobility of such atoms of hydrogen in different compounds.

EXPERIMENTAL

Preparation of deuterated dimethylanilines

1. 4-$C_6H_4DN(CH_3)_2$ was synthesized by the following scheme

$$C_6H_5N(CH_3)_2 \xrightarrow{Br_2} 4\text{-}C_6H_5BrN(CH_3)_2\ [4] \xrightarrow{LiBu} 4\text{-}C_6H_4LiN(CH_3)_2\ [5] \xrightarrow{D_2O} 4\text{-}C_6H_4DN(CH_3)_2.$$

2. 2,4,6-$C_6H_2D_3N(CH_3)_2$ was prepared by isotope exchange of dimethylaniline with deuteroethanol catalyzed by sulfuric acid [6].

3. 2,6-$C_6H_3D_2N(CH_3)_2$ was prepared from the preceding compound by the same scheme as the first compound, with H_2O employed in the last stage instead of D_2O.

4. 3,5-$C_6H_3D_2N(CH_3)_2$ was synthesized by the following route:

$$C_6H_6 \xrightarrow{ND_3 + ND_2^-} C_6D_6\ [7] \xrightarrow{HNO_3} C_6D_5NO_2\ [8] \xrightarrow{Sn + HCl} C_6D_5NH_2\ [8] \xrightarrow{CH_3OH + H_2SO_4}$$

$$\longrightarrow C_6D_5N(CH_3)_2\ [9] \xrightarrow{CH_3COOH} 3,5\text{-}C_6H_3D_2N(CH_3)_2.$$

In the course of the methylation it was possible to wash out the deuterium atoms from the ortho and para positions. For complete exchange of these atoms the material was heated twice for 10 hours at 120° with 100 times (on the basis of moles) its amount of glacial acetic acid [10].

5. $C_6D_5N(CD_3)_2$ was prepared by deuterium exchange with $ND_3 + KND_2$ (0.5 N) in the course of 35 days at room temperature.

6. 3,5-$C_6H_3D_2N(CD_3)_2$ was obtained from the preceding compound by washing the deuterium from the 2,4, and 6 positions with glacial acetic acid.

Measurement of rate constant of deuterium exchange

The deuterated preparations were diluted with ordinary dimethylaniline so that the concentration of deuterium in the water from combustion of the compound was 4-6 atom-%. The index of refraction of all the compounds before and after the experiments was n_D^{20} 1.5580 ± 0.0002.

To a weighed 0.3-g sample of compound was added 10 ml of potassamide solution (0.058-0.059 N). The experiments were carried out at 25 ± 0.1°. The reaction was interrupted by cooling the solution to -78° and adding ammonium chloride or pouring the solution into water.

The results of the measurements are given in Tables 1-7, in which the following abbreviations are used: c_w^0 = = concentration of deuterium (atom-%) in water from combustion of compound before experiment; c_w = the same after experiment; τ = duration of experiment in hours; k_{ave} = rate constant of total exchange reaction; k_{ortho}, k_{meta}, k_{para}, $k_{N(CD_3)_2}$ = rate constants of exchange of deuterium atoms in the respective positions indicated.

The rate constants were calculated from the first order equation $K = \frac{2.3}{\tau} \log \frac{c_w^0}{c_w}$ and were expressed in sec^{-1}. The use of such a simplified formula was permissible, since there were about 500 H atoms for 1 D atom.

RESULTS OF MEASUREMENTS

The experiments on the determination of the rate of exchange of a deuterium atom in the para position are presented in Table 1.

TABLE 1. Experiments with 4-$C_6H_4DN(CH_3)_2$ (c_w^0 = 5.44 atom-% D)

τ (min)	c_w	$k_{para} \cdot 10^5$
15	3.07	1.1
15	3.07	1.1
15	3.12	1.0
20	2.36	1.2
20	2.42	1.1
20	2.52	1.1

TABLE 2. Experiments with 2,4,6-$C_6H_2D_3N(CH_3)_2$ (c_w^0 = 5.62 atom-% D); (c_w^0 (ortho) = 3.74 atom-% D)

τ (hr)	c_w	$k_{av.} \cdot 10^5$	c_w (ortho)	$k_{ortho} \cdot 10^4$
0.5	4.21	16	2.38	2.5
1	3.35	14	1.57	2.4
4	1.78	8.0	0.19	2.2
4	1.74	8.1	0.15	2.2
4	1.83	7.8	0.22	2.1
6	1.53	6.0	0.04	2.2
6	1.56	6.0	0.06	2.0
6	1.54	6.0	0.05	2.1

From the data of Table 2 it is seen that K_{ave}, the averaged constant of the rate of exchange of deuterium in 2,4,6-$C_6H_2D_3N(CH_3)_2$, decreased with time but always remained greater than k_{para}. This can be explained only by the fact that as the duration of the experiments was increased, there was more and more appreciable participation in the exchange reaction by the less reactive para atom in addition to the ortho atom. Knowing k_{para} (Table 1), we calculated for each of the experiments the change in concentration of deuterium resulting from the exchange of the para atom and were able to establish k_{ortho} by using the initial concentration c_w (ortho) - 2/3 c_w^0, and c_w^0 (para) = = $c_w^0/3$.

For a check, several measurements were carried out with the compound 2,6-$C_6H_3D_2N(CH_3)_2$, from which a similar value of k_{ortho} was obtained (Table 3).

The rate of exchange of the meta atoms of deuterium was established by measurements carried out with 3,5-$C_6H_3D_2(CH_3)_2$ (Table 4).

With k_{meta} known, it was possible to calculate that when the duration of the experiment was 40 hr, the time was sufficient for the exchange for protium of practically all the deuterium present in the meta positions. In experiments lasting 52 and 60 hr, therefore, it was perfectly permissible to deduct from the initial concentration of deuterium that part of it ($0.25c_w^0$) which belonged to the meta atoms and to calculate the rate constants for the exchange of deuterium in the dimethylamino group ($k_{N(CD_3)_2}$). For the results see Table 5.

In order to calculate the factors of the partial rate of deuterium exchange in the dimethylaniline molecule, parallel experiments were set up with deuterobenzene under the same conditions (Table 6).

The rate constant $K_{C_6D_6} = 1.5 \times 10^{-4}$ sec^{-1} is close in magnitude to the constant obtained in reference [7] ($k_{C_6H_6} = 1.7 \times 10^{-4}$ sec^{-1}).

TABLE 3. Experiments with 2,6-$C_6H_3D_2N(CH_3)_2$ (c_w^0 = 3.7 atom-% D)

τ (hr)	c_w	$k_{ortho} \cdot 10^4$
1	1.71	2.2
1	1.86	2.0
1	1.75	2.1

TABLE 4. Experiments with 3,5-$C_6H_3D_2N(CH_3)_2$ (c_w^0 = 4.19 atom-% D)

τ (hr)	c_w	$k_{meta} \cdot 10^5$
4	2.88	2.7
4	2.86	2.6
4	2.98	2.4
4	2.90	2.6
4	2.90	2.6
5.5	2.69	2.2
5.5	2.72	2.2
5.5	2.69	2.2

TABLE 5. Experiments with 3,5-$C_6H_3D_2N(CD_3)_2$ (c_w^0 = 6.66 atom-% D)

τ (hr)	c_w	$k_{N(CD_3)_2} \cdot 10^6$
52	3.48	1.9
52	3.50	1.9
60	3.36	1.8
60	3.18	2.2

TABLE 6. Experiments with C_6D_6 (c_w^0 = 3.53 atom-% D)

τ (hr)	c_w	$k_{C_6D_6} \cdot 10^4$
4	0.39	1.5
4	0.34	1.6

TABLE 7. Average Values of Rate Constants of Deuterium Exchange of Nonequivalent Atoms in the Dimethylaniline Molecule and Factors of Partial Rate of Deuterium Exchange

Isomer	k	f
Ortho	$2.1 \cdot 10^{-4}$	1.4
Meta	$2.4 \cdot 10^{-5}$	$1.6 \cdot 10^{-1}$
Para	$1.1 \cdot 10^{-5}$	$7 \cdot 10^{-2}$
$N(CD_3)_2$	$2.0 \cdot 10^{-6}$	$1.3 \cdot 10^{-2}$

TABLE 8. Experiments with 2,6-$C_6H_3D_2N(CH_3)_2$ and Glacial Acetic Acid (c_w^0 = 3.7 atom-% D)

τ (min)	c_w	$k_{ortho} \cdot 10^4$
30	2.45	2.34
60	1.65	2.31
60	1.67	2.28

In Table 7 a summary is given of the average values of the rate constants of exchange of the nonequivalent atoms of deuterium in the dimethylaniline molecule (when c_{KNH_2} = 0.058 N at 25°) and the magnitudes of the factors of the partial rate f.

TABLE 9. Data Characterizing Electron-Acceptor and Electron-Donor Properties of Substituents

Group	μ	δ_{para}	$\Delta\lambda_1$	$\Delta\lambda_2$	k_{rel}	σ_{para}
NO_2	−4.01	+0.42	3	103	$2 \cdot 10^{-6}$	+0.778
$N(CH_3)_2$	+1.61	−0.50	101	10	$5 \cdot 10^{18}$	−0.600
OCH_3	+1.28	−0.23	40	−5	$1 \cdot 10^{9}$	−0.268
OC_6H_5	—	—	—	—	$1 \cdot 10^{7}$	−0.028

It seemed to us very desirable to compare directly the rules for basic and acid deuterium exchange in the dimethylaniline molecule. E. N. Zvyagintseva in our laboratory measured the rate of isotopic exchange of the para atom of deuterium in 4-$C_6H_4DN(CH_3)_2$ with glacial CH_3COOH at 90° and found that $k_{para} = 1.70\ (\pm 0.05) \times 10^{-4}$. To measure the rate of exchange of the ortho atoms we carried out similar experiments with 2,6-$C_6H_3D_2N(CH_3)_2$.

The ratio between the number of moles of solvent and compound also was 50. The results of the experiments are given in Table 8.

Consequently, with glacial acetic acid the ortho atoms of hydrogen were exchanged 1.4 times as fast as the para atoms. The meta atoms of hydrogen in the dimethylaniline did not participate in the exchange reaction with the acid even in long experiments.

DISCUSSION OF RESULTS

As has been reported, the dimethylamino group usually is one of the substituents with the most strongly expressed electron-donor properties. In Table 9 data from the literature have been collected with respect to some physical properties and chemical reactions of aromatic compounds containing $N(CH_3)_2$, OCH_3, and OC_6H_5 groups. Comparison of these data among themselves and with the corresponding values for the nitro group, which is one of the most electronegative substituents, shows a decrease in electron-donor properties in the order: $N(CH_3)_2 > OCH_3 > OC_6H_5$.

In Table 9 the following abbreviations are used: μ = dipole moment of aromatic compounds with the indicated substituents [11]; δ_{para} = magnitude of "chemical shift", determined by means of measurement of nuclear magnetic resonance, characterizing the relative electron density of the para atom of the carbon ring [12]; $\Delta\lambda_1$ and $\Delta\lambda_2$ = magnitudes of shift of absorption band in electron spectrum when a second substituent is introduced in the para position in nitrobenzene and dimethylaniline, respectively [13]. The more the substituents in the compounds formed differ in their nature, the greater these values are; k_{rel} = approximate values of rate constants of bromination of aromatic compounds referred to the rate constant of bromination of benzene [14]; σ_{para} = Hammett's constant [15], which permits quantitative evaluation of the effect of a substituent on the reactivity of a side group in the para position [16].

The rate of electrophilic replacement of hydrogen increases with a strengthening of the electron-donor properties of the substituent. Thus, dimethylaniline is brominated at a rate 9 orders greater than anisole, and 11 orders more rapidly than diphenyl ether, while nitrobenzene is brominated 24 orders more slowly than dimethylaniline.

A similar phenomenon is observed also for the acid isotope exchange of hydrogen in aromatic compounds, which is subject to the rules that are common to other reactions of electrophilic substitution of hydrogen [1]. For example, isotope exchange of hydrogen in anisole was not noted when a solution was heated in glacial acetic acid, even in the course of two days at 90° [17], while in dimethylaniline at the same temperature, exchange of hydrogen proceeds at a rate the constant of which is of the order of 10^{-4} sec^{-1} [10]. The exchange of hydrogen in nitrobenzene with liquid hydrogen bromide goes exceptionally slowly even in the presence of aluminum bromide [18].

Although electron-donor groups orient electrophilic substitution to the ortho and para positions as a result of the increase in electron density at the corresponding carbon atoms and the dimethylamino group is one of the strongest electron donors, when dimethylaniline is nitrated, depending on the reaction conditions, more or less appreciable substitution is observed in the meta position [19, 20]. This is explained by the fact that in the course of the substitution reaction the electrophilic reagent can add to the coordination-unsaturated nitrogen atom of the dimethylamino group and convert it to a positively charged ion, which orients the electrophilic substitution to the meta position. In order to exclude this complication, it is necessary to avoid a change in valence of the nitrogen. This is achieved practically in the acid exchange of hydrogen in dimethylaniline with acetic acid, since a salt is not formed between

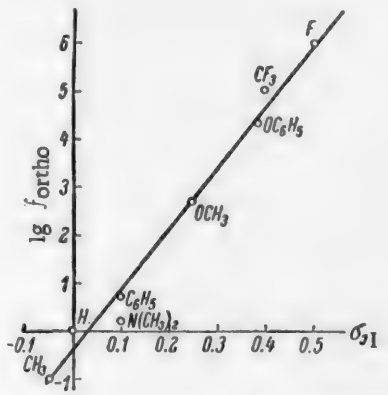
them, but rather a molecular compound without any essential change in valence of the nitrogen [10,21]. Hence the experiments on deuterium exchange with acetic acid apparently give a correct idea of the relative reactivity of the ortho and para positions in the dimethylaniline molecule.

We found that at 90° the ortho atom exchanges somewhat more rapidly than the para atom (k_{ortho}/k_{para} = = 1.4). According to Satchell's measurements [22] for anisole this ratio is 0.55 for deuterium exchange with a solution of sulfuric acid in glacial acetic acid and 0.42 for deuterium exchange with 8.5 M aqueous solution of sulfuric acid. Lauer and Day [23] pointed out that for deuterium exchange with a solution of sulfuric acid in acetic acid the ratio k_{ortho}/k_{para} = 0.52 (at 100°) and 0.33 (at 80°). Thus in anisole, in contrast to dimethylaniline, the para position is more reactive than the ortho position.

In Table 10 a summary is given of the values of the factors of the partial rate of isotope exchange with a base or with an acid for the ortho, meta, and para deuterium atoms in the molecules of dimethylaniline, anisole [2,24,25], and diphenyl ether [2]. In the exchange reaction with a base (NH_3 + KNH_2) the reactivity of the CH bonds in the dimethylaniline molecule decrease as they are removed further from the substituent ($f_{ortho} > f_{meta} > f_{para}$), the same as happens in deuterium exchange with anisole and diphenyl ether. In acid deuterium exchange and in other electrophilic substitution reactions the meta atoms are replaced at a rate several orders lower than the ortho and para atoms or even are practically not replaced at all.

TABLE 10. Comparison of Factors of Partial Rate of Deuterium Exchange

Group	Reagent	Ortho	Meta	Para
$N(CH_3)_2$	$NH_3 + KNH_2$	1.5	0.2	0.07
	CH_3CO_2H	[$2.2 \cdot 10^{-4}$]	—	[$1.7 \cdot 10^{-4}$]
OCH_3	$NH_3 + KNH_2$	500	1 **	0.5
	H_2SO_4 (8.5 M)	23000	0.25 ***	55000
OC_6H_5	$NH_3 + KNH_2$	20000	50	4
	Nitration	117	—	234



The stronger electron donor the substituent is [$N(CH_3)_2$ > OCH_3 > OC_6H_5] and the more it accordingly activates the reactions of electrophilic substitution of hydrogen in the aromatic ring as a result of conjugation, the more weakly does the same substituent activate reactions of protophilic substitution of hydrogen, causing an inductive shift of electrons as an electron acceptor. The inductive effect first of all should be detected very close to the substituent, i.e., in the ortho position. Therefore we should compare the values of f_{ortho} for deuterium exchange with a solution of potassamide in liquid ammonia.

The factor of the partial rate of replacement of deuterium in the ortho position of dimethylaniline is 700 times less than in the corresponding position in anisole and 10 times less than in diphenyl ether. From the values presented for the ratio f_{ortho}/f_{para} it is seen also that when the electron-donor properties of the substituent become stronger, the reactivities of the ortho and para CH-bonds converge, while in acid exchange this ratio is close to unity.

	$N(CH_3)_2$	OCH_3	OC_6H_5
$f_{ortho}/f^{N(CH_3)_2}_{ortho}$	1	300	10000
$(f_{ortho}/f_{para})_{base}$	20	1000	5000
$(f_{ortho}/f_{para})_{acid}$	1.4	0.4	(0.5)*

* The rate constants are enclosed in square brackets. Data are lacking on acid exchange for diphenyl ether. According to Dewar [26], when diphenyl ether is nitrated in acetic anhydride at 25°, equal amounts of ortho and para isomers are obtained, and the meta is absent: f_{ortho} = 117, f_{para} = 234.

** According to the data of [25].

*** 10.4 M perchloric acid solution.

* For nitration.

Further, the stronger electron donor the substituent is, the less distant from it is the hydrogen atom, for which $f < 1$ in deuterium exchange with a base.

$N(CH_3)_2$	OCH_3	OC_6H_5
$f_{meta} < 1$	$f_{para} < 1$	$f_{para} > 1$

This fact may be explained in the following fashion: the relative acidity of the hydrogen atoms depends on the participation in the distribution of the electron density around the carbon atoms of the chain not only by the σ, but also by the π electrons, and the more weakly the inductive effect of the substituent is expressed, the more strongly the conjugation effect appears [25, 27].

The basis for the fact that it is precisely the inductive effect that predominantly determines the rate of exchange of the ortho hydrogen atoms with a base is the existence of a linear relationship between $\log f_{ortho}$ and the inductive parameters of the substituents, σ_I (Table 11 and figure) according to Taft [28], for all compounds with which determinations had been carried out, up to that time, of the factors of the partial rate of exchange in ammoniacal solutions of potassamide. The proportionality between $\log f_{ortho}$ and pK_i, where K_i is the ionization constant of substituted acetic acid, has been established previously [2].

TABLE 11. Values of $\log f_{ortho}$ and Taft's Inductive Parameters

Substituent	F	CF_3	OC_6H_5	OCH_3	C_6H_5	$N(CH_3)_2$	H	CH_3
σ_I	0.52	0.41	0.38	0.25	0.10	0.10	0.00	—0.05
$\log f_{ortho}$	6.0	5.0	4.3	2.7	0.7	0.2	0.0	—1
Reference	[25]	[25]	[2]	[2,24]	[33]	—	—	[34]

As would be expected, in deuterium exchange with a base as also in metallization [29] the rate of replacement of the ortho hydrogen atom increases in order from dimethylaniline to anisole and fluorobenzene in conformance with the increase in affinity for the electron of the atoms of nitrogen, oxygen, and fluorine. In the compounds mentioned, the ortho hydrogen atom is replaced most rapidly in both reactions [30-32].

Let us now compare the mobility of the hydrogen atoms in the methyl group directly attached to the aromatic ring (in toluene) and in a group attached to the ring through an oxygen atom (in anisole) or nitrogen atom (in dimethylaniline).

Group	f
CH_3	70
OCH_3	0.250
$N(CH_3)_2$	0.013

Consequently, the hydrogen of the methyl group of toluene is exchanged more than 5000 times more rapidly, and that in the methoxy group 20 times more rapidly than the one in dimethylaniline. In order to arrive at definite conclusions regarding the nature of the phenomenon under consideration, we plan to study compounds containing sulfur and selenium (if they prove to be stable toward a solution of potassamide in ammonia), and also to determine how the mobility of the hydrogen atom of the methyl group changes when a second substituent is introduced into the aromatic ring and when the benzene ring is replaced by the naphthalene nucleus.

SUMMARY

1. Preparations of deuterodimethylaniline have been made containing deuterium in different positions: 4-$C_6H_4DN(CH_3)_2$; 2,6-$C_6H_3D_2N(CH_3)_2$; 3,5-$C_6H_3D_2N(CH_3)_2$; 2,4,6-$C_6H_2D_3N(CH_3)_2$; 3,5-$C_6H_3D_2N(CD_3)_2$; $C_6D_5N(CD_3)_2$.

2. Measurements have been made of the rate of isotope exchange with a solution of potassamide in liquid ammonia of deuterium atoms in the dimethylaniline molecule in the ortho, meta, and para positions and in the dimethylamino group, and also in deuterobenzene, and the factors of the partial rate of exchange have been determined ($f_{ortho} = 1.4$; $f_{meta} = 1.6 \times 10^{-1}$; $f_{para} = 7 \times 10^{-2}$; $f_{N(CD_3)_2} = 1.3 \times 10^{-2}$).

3. Measurements have been made of the rate of exchange of the ortho deuterium atoms in the dimethylaniline molecule with glacial acetic acid ($k_{90°} = 2.3 \times 10^{-4}$ sec^{-1}). It has been found that $k_{ortho}/k_{para} = 1.4$.

4. It has been shown that the $N(CH_3)_2$, OCH_3, and OC_6H_5 groups can react in a dual manner – as electron-donors in acid hydrogen exchange and as electron acceptors in base exchange in the aromatic ring. The $N(CH_3)_2$ group, which is the strongest of them as an electron donor, reacts as the weakest electron acceptor.

5. It has been established that the linear relationship of f_{ortho} (for exchange with a base) to the inductive parameters of Taft is in general applicable also to the $N(CH_3)_2$ group.

6. The relative mobility of the hydrogen atoms in methyl groups directly attached to the aromatic ring in toluene (5000) and separated from the ring by an atom of oxygen in anisole (20) or by an atom of nitrogen in dimethylaniline (1) has been determined.

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A STUDY OF THE ACID-BASE REACTION BETWEEN AROMATIC AMINES AND CARBOXYLIC ACIDS BY THE DEUTERIUM EXCHANGE METHOD*

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According to Brönsted [1] the acid-base reaction consists of the migration of a proton of the acid to the base, and consequently ions always are formed in the reaction between electroneutral protolytes. Bronsted's theory, which was formulated about forty years ago, has proved to be very fruitful and has received general recognition [2]. New experimental facts, however, have revealed the inadequacy of this theory for the description of reactions between acids and bases. On the one hand, deviations from the quantitative rules of the Brönsted theory have disclosed [3] the considerably greater complexity of the processes that take place in the ionization of protolytes than follows from the ideas of Brönsted. On the other hand, with the aid of more sensitive methods in comparison with those which were used previously, acid and basic properties have been established for compounds, in particular hydrocarbons, which according to Brönsted were aprotonic, i.e., compounds incapable of participating in protolytic reactions. Such a sensitive method is that developed in our laboratory for the study of isotopic exchange reactions of hydrogen in very protophilic and very protogenic media, which permits quantitative evaluation of the relative strength of such weak acids and bases as the hydrocarbons [4].

The mechanism of the reactions between very weak and between very strong protolytes is not the same. The reaction of the latter leads to ionization, but the reactions between weak protolytes, as has been shown by infrared spectroscopy [5], are limited by the formation of a hydrogen bond. According to N. D. Sokolov [6] this is always the first stage of the transfer of a proton.

It was necessary to introduce modifications into the definition of acids and bases. The following definitions have been proposed for consideration [4]: a base is an electron donor reagent which has an affinity for the proton; and acid is an electron acceptor reagent, a hydrogen of which participates in an equilibrium reaction with a base (the acid combines with the base through a hydrogen bond or yields a proton to it).

The present investigation was devoted to the study of the acid-base reaction in aromatic amine – carboxylic acid systems by the deuterium exchange method. The aromatic amines have a dual reaction capacity with respect to acids [7]. The latter can react both with the nitrogen atom of the amine and with the ortho and para hydrogen atoms on which the electron density is increased because of the conjugation of the p-electrons of the nitrogen atom with the π-electrons of the ring. When there is a difference in the isotope composition of the hydrogen of the acid and of the aromatic rings of the amine, hydrogen exchange can occur in them [8-11]. The rate of exchange should increase with an increase in the strength of the acid in accord with the usual rules of acid hydrogen exchange [4] in the absence of ionization of the nitrogen atom. If, however, the addition of a proton to the nitrogen changes its valence state in the direction of the formation of a tetravalent positively charged nitrogen ion, then the conjugation will be destroyed and this will inhibit the exchange reaction. Thus, by measuring the kinetics of the deuterium exchange between different amines and acids it is possible to follow the change in the nature of the acid-base reaction.

We measured the kinetics of deuterium exchange between p-deuterodimethylaniline, p,p'-dideuteromethyldiphenylamine, and triphenylamine containing deuterium in all the ortho-para positions and anhydrous carboxylic acids (acetic, formic, monochloro-, trichloro-, and trifluoroacetic) differing considerably in strength (their dissociation constants in aqueous solution cover a range of five orders).

* Preliminary communication published in ZhOKh 29, 1751 (1959).

Judged by the data from physicochemical analysis [12, 13], dimethylaniline reacts as a nitrogenous base with all of the acids enumerated, including acetic acid. According to Bronsted in this case a proton should add to the nitrogen atom and form a salt. In the literature, however, there are indications that in the acid-base reaction of dimethylaniline (or aniline) with acetic acid (or with acids similar to it in strength) not a salt, but a slightly polar molecular compound is formed. This is indicated by measurements of the electron [14] and the vibrational [15] spectra, data from physicochemical analysis of the systems [16], and kinetic measurements [17]. In such a case, in departure from Bronsted's scheme, the valence state of the nitrogen in the dimethylaniline is not the same in reactions with acids that differ in strength. An increase in strength of the acid (or a rise in its dielectric constant) will be accompanied by a decrease in the rate of deuterium exchange, since conversion of the nitrogen atom to the tetravalent positively charged nitrogen ion will then become more likely.*

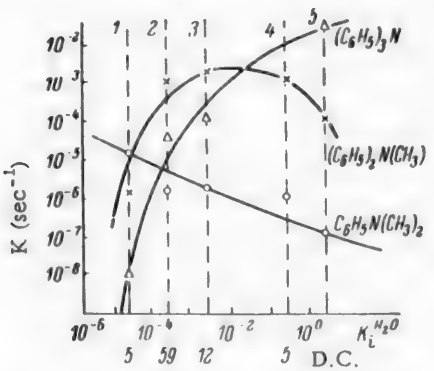
In Table 1 are shown the dissociation constants of the acids in water $K_a^{H_2O}$, the average values of the acidity function H_0 of the acids in the anhydrous state, and their dielectric constants, and the average values of the constants for the rate of exchange of the para deuterium atom in the dimethylaniline molecule with all the acids mentioned also are given. In going from acetic to trifluoroacetic acid the rate constants decrease almost by two orders and the activation energy of the exchange reaction E increases correspondingly by 8 Cal/mole. The logarithm of the coefficient (log A) for the reactions with all the acids except acetic is practically the same (log A = 13), but for the exchange reaction with acetic acid it is less by three orders.

TABLE 1. Experiments with Dimethylaniline

Acid	$K_a^{H_2O}$	$-H_0$	Dielectr. const. (temp.)	$k_{75°}$	$k_{90°}$	$k_{115°}$	E	lg A
CH_3COOH	$2 \cdot 10^{-5}$	—	6 (25)	$4 \cdot 10^{-5}$	$2 \cdot 10^{-4}$	$1 \cdot 10^{-3}$	22.4	9.7
$HCOOH$	$2 \cdot 10^{-4}$	2	59 (16)	$5 \cdot 10^{-6}$	$3 \cdot 10^{-5}$	$4 \cdot 10^{-4}$	29.7	13.3
$CH_2ClCOOH$	$2 \cdot 10^{-3}$	1	12 (80)	$1 \cdot 10^{-5}$	$7 \cdot 10^{-5}$	$8 \cdot 10^{-4}$	28.2	12.8
CCl_3COOH	$2 \cdot 10^{-1}$	—	5 (61)	$5 \cdot 10^{-7}$	$3 \cdot 10^{-5}$	$4 \cdot 10^{-4}$	29.2	13.1
CF_3COOH	$2 \cdot 10^{0}$	4	8; 40 (20)**	$8 \cdot 10^{-7}$	$6 \cdot 10^{-6}$	$8 \cdot 10^{-5}$	30.8	13.3

* Distinctly different values of the dielectric constant are given in two reports [19,20].

The greater the number of phenyl groups connected to the nitrogen atom, the less electronegative are the ortho-para carbon atoms of the amine and the weaker nitrogenous base it is. Thus, the dissociation constants of dimethylaniline and diphenylamine [21] are 2×10^{-10} and 8×10^{-14}, respectively, and triphenylamine is still a much weaker base ($K_b^{H_2O}$ was not measured). According to the data from physicochemical analysis, diphenylamine [22] does not react with acetic and chloroacetic acids and gives a compound with stronger acid (trichloroacetic), while triphenylamine [23] does not react even with perchloric and other very strong mineral acids.



Relation of rate constants of deuterium exchange in aromatic amines to acidity of the medium. 1) CH_3COOH, 2) $HCOOH$, 3) $CH_2ClCOOH$, 4) CCl_3COOH, 5) CF_3COOH.

In the figure the rate constants of deuterium exchange measured at 65° or calculated for this temperature are plotted against the dissociation constants of the acids in water ($K_i^{H_2O}$), the values of which to a great extent characterize the order of the change in strength of the anhydrous acids. We see that while the curve for dimethylaniline runs downward as a result of the increase in polarity of its compounds with the acids as they increase in strength**, the curve for triphenylamine rises steadily, since with this amine even trifluoroacetic acid does not form a compound. The curve for methyldiphenylamine passes through a maximum because it is a base intermediate in strength, and like triphenylamine does not react with the first members of the series of acids, but like dimethylaniline it forms polar compounds with trichloro- and trifluoroacetic acids.

* See the work of Barrow [18], who studied by the infrared method the products of the reaction of pyridine with carboxylic acids of different strengths in a nonpolar solvent.

** This interpretation of the results is confirmed also by the increase in the activation energy of the exchange reaction when the strength of the acid increases.

The order of the rates of deuterium exchange of the three amines with acetic and with trifluoroacetic acids are diametrically opposite (See also Table 2), as would be expected if we assume that the rate of the exchange reaction depends on the relative electronegativity of the ortho-para carbon atoms. On solution in glacial acetic acid only dimethylaniline gives a compound, and moreover it is only slightly polar and therefore the order is preserved which corresponds to the decrease in electronegativity of the aromatic rings in the amine with an increase in their number. The strength of trifluoroacetic acid is insufficient for the conversion only of triphenylamine to a salt, but dimethylamine and even methyldiphenylamine are ionized. The stronger base the aromatic amine is, and consequently the more intense its reaction with the acid, the less likely is an increase in the electron density at the ortho-para carbon atoms as a result of conjugation. Therefore deuterium exchange proceeds most rapidly with triphenylamine and most slowly with dimethylaniline. In this connection we note that in experiments on deuterium exchange with a still stronger acid, liquid deuterium bromide [24], all nine ortho-para hydrogen atoms in the triphenylamine molecule are exchanged in less than five minutes at room temperature, while with dimethylaniline the exchange reaction was not noted even after the lapse of more than 1000 hours. An increase in acidity of the medium by addition of aluminum bromide to liquid DBr sharply decreases the rate of exchange of hydrogen in triphenylamine.

TABLE 2. Rate Constants of Deuterium Exchange

Amine	CH_3COOH		HCOOH		$CH_2ClCOOH$		CCl_3COOH		CF_3COOH	
	°C	k	°C	k	°C	k	°C	k	°C	k
$C_6H_4DN(CH_3)_2$	115	$1 \cdot 10^{-3}$	65	$(3 \cdot 10^{-6})$	65	$(4 \cdot 10^{-6})$	65	$(2 \cdot 10^{-6})$	30	$(1 \cdot 10^{-9})$
$(C_6H_4D)_2NCH_3$	115	$1 \cdot 10^{-4}$	65	$1 \cdot 10^{-3}$	65	$4 \cdot 10^{-3}$	65	$2 \cdot 10^{-3}$	30	$(1 \cdot 10^{-6})$
$(C_6H_2D_3)_3N$	115	$3 \cdot 10^{-6}$	65	$[6 \cdot 10^{-5}]$	65	$1 \cdot 10^{-4}$	65	$\sim 10^{-2}$***	30	$2 \cdot 10^{-3}$

* The values of k in parentheses were calculated on the basis of the determination of the energy of activation. The value of k in brackets was determined approximately from the ratio of the rate constants at two temperatures.

** The exchange reaction reached equilibrium in less than 5 minutes.

A change in valence state of the nitrogen, which we are convinced causes a suppresion of acid deuterium exchange in aromatic amines, is conducive to base deuterium exchange in nitrogenous methylated heterocycles proceeding in alcoholic solutions [25,26]. The results obtained graphically illustrate the position that the ionization of a base when it reacts with an acid and the formation of a hydrogen bond between them are phenomena of the same category.

Qunaldine is a base similar in strength to dimethylaniline, and the alcohols are extremely weak acids [27] ($K_a^{H_2O} = 10^{-15}$-10^{-16}). The acid-base reaction of quinaldine with alcohols is limited by the formation of a hydrogen bridge between the nitrogen atom of the heterocycle and the oxygen of the hydroxyl group of the alcohol. This has been demonstrated [5] by measurements of the infrared spectra which revealed a considerable shift in the frequency of the band of the O-H bond of the alcohol. Furthermore, by measurements of the dipole moments and the infrared spectra it was established [28] that the polarity of the hydrogen bond depends on the relative acidity of the alcohols, which was independently determined with the aid of indicators [29].

An increase in polarity of the hydrogen bond corresponds to an increase in the positive charge of the nitrogen atoms of the heterocycle and a stronger movement toward it of the electrons of the C-H bonds of the methyl group, as a result of which the hydrogen atoms become more mobile. A direct relationship has been observed [25] between the rate of exchange of the hydrogen in the methyl group of quinaldine and the acidity of the alcohol. The reaction is accelerated still more when the solution of quinaldine in the alcohol is acidified with hydrochloric acid, since the strong acid drives the nitrogenous base to ionization.

The results of investigation of the acid-base reaction by the deuterium exchange method, like many other facts known at the present time [4], indicate that Bronsted's scheme does not embrace the entire field of reactions between acids and bases in view of which a change in their definition is necessary.

TABLE 3. Experiments with Dimethylaniline (C_0 = 5.11; C_∞ = 0.23)

Acid	75°			90°			115°		
	t	C_t	k	t	C_t	k	t	C_t	k
CH_3COOH	2hr 38min	3.55	$4.1 \cdot 10^{-5}$	1hr	2.90	$1.7 \cdot 10^{-4}$	10min	2.58	$1.2 \cdot 10^{-3}$
	4hr 25min	2.68	$4.3 \cdot 10^{-5}$	1hr 30min	2.25	$1.6 \cdot 10^{-4}$	10min	2.58	$1.2 \cdot 10^{-3}$
	—	—	—	1hr 30min	2.22	$1.7 \cdot 10^{-4}$	15min	1.98	$1.1 \cdot 10^{-3}$
	—	—	—	2hr	1.58	$1.8 \cdot 10^{-4}$	—	—	—
HCOOH	31hr	2.88	$5.5 \cdot 10^{-6}$	7hr	2.75	$2.6 \cdot 10^{-5}$	25min	2.33	$5.6 \cdot 10^{-4}$
	31hr	3.07	$4.9 \cdot 10^{-6}$	9hr	2.11	$2.9 \cdot 10^{-5}$	25min	3.04	$3.7 \cdot 10^{-4}$
	30hr 20min	3.14	$4.7 \cdot 10^{-6}$	11hr	1.92	$2.7 \cdot 10^{-5}$	35min	2.48	$3.7 \cdot 10^{-4}$
	—	—	—	11hr	1.96	$2.6 \cdot 10^{-5}$	55min	1.33	$4.5 \cdot 10^{-4}$
$CH_2ClCOOH$	10hr	3.46	$1.2 \cdot 10^{-5}$	3hr	2.66	$6.5 \cdot 10^{-5}$	15min	2.56	$8.2 \cdot 10^{-4}$
	10hr	3.41	$1.2 \cdot 10^{-5}$	4hr	2.13	$6.6 \cdot 10^{-5}$	20min	2.25	$7.4 \cdot 10^{-4}$
	15hr	2.84	$1.2 \cdot 10^{-5}$	5hr	1.69	$6.7 \cdot 10^{-5}$	20min	2.22	$7.5 \cdot 10^{-4}$
	—	—	—	6hr	1.41	$6.6 \cdot 10^{-5}$	24min	1.74	$8.2 \cdot 10^{-4}$
CCl_3COOH	21hr 10min	3.50	$5.2 \cdot 10^{-6}$	6hr	2.70	$3.2 \cdot 10^{-5}$	30min	2.53	$4.2 \cdot 10^{-4}$
	21hr 20min	3.46	$5.4 \cdot 10^{-6}$	8hr	2.30	$3.0 \cdot 10^{-5}$	35min	2.30	$4.1 \cdot 10^{-4}$
	30hr	3.09	$5.0 \cdot 10^{-6}$	8hr	2.25	$3.1 \cdot 10^{-5}$	40min	1.95	$4.3 \cdot 10^{-4}$
	—	—	—	10hr	1.92	$3.0 \cdot 10^{-5}$	52min	1.74	$3.8 \cdot 10^{-4}$
	—	—	—	—	—	—	52min	1.63	$4.0 \cdot 10^{-4}$
CF_3COOH	53hr 20min	4.34	$8.9 \cdot 10^{-7}$	10hr	4.30	$5 \cdot 10^{-6}$	2 hr 30min	2.37	$9 \cdot 10^{-5}$
	75hr 50min	4.10	$8.5 \cdot 10^{-7}$	11hr	3.89	$7 \cdot 10^{-6}$	2 hr 30min	2.86	$7 \cdot 10^{-5}$
	99hr 50min	3.94	$7.6 \cdot 10^{-7}$	11hr 13min	4.10	$6 \cdot 10^{-6}$	3 hr	2.36	$8 \cdot 10^{-5}$
	99hr 50min	3.94	$7.6 \cdot 10^{-7}$	11hr 15min	4.21	$5 \cdot 10^{-6}$	3 hr 30min	1.96	$8 \cdot 10^{-5}$
	—	—	—	11hr 31min	4.15	$5 \cdot 10^{-6}$	5 hr 12min	1.37	$8 \cdot 10^{-5}$
	—	—	—	11hr 43min	4.21	$5 \cdot 10^{-6}$	—	—	—
	—	—	—	11hr 44min	4.00	$6 \cdot 10^{-6}$	—	—	—

TABLE 4. Experiments with Methyldiphenylamine (C_0 = 6.03; C_∞ = 0.29; C_0 = 5.13*; C_∞ + 0.25*)

Acid	75°			90°			115°		
	t	C_t	k	t	C_t	k	t	C_t	k
CH_3COOH**	26 hr	4.11	$4.2 \cdot 10^{-6}$	4 hr 27 min	4.53	$1.9 \cdot 10^{-5}$	1 hr	3.81	$1.4 \cdot 10^{-4}$
	32 hr	3.87	$4.1 \cdot 10^{-6}$	5 hr 26 min	4.38	$1.7 \cdot 10^{-5}$	1 hr 37 min	3.02	$1.3 \cdot 10^{-4}$
	38 hr	3.41	$4.5 \cdot 10^{-6}$	5 hr 27 min	4.41	$1.7 \cdot 10^{-5}$	1 hr 39 min	2.87	$1.4 \cdot 10^{-4}$
	38 hr	3.32	$4.7 \cdot 10^{-6}$	—	—	—	—	—	—
					65°				
HCOOH	—	—	—	17 min	2.00	$1.2 \cdot 10^{-3}$	—	—	—
	—	—	—	18 min	2.13	$1.1 \cdot 10^{-3}$	—	—	—
	—	—	—	25 min	1.34*	$1.0 \cdot 10^{-3}$	—	—	—
$CH_2ClCOOH$	—	—	—	7 min	1.16*	$4.0 \cdot 10^{-3}$	—	—	—
	—	—	—	7 min	1.28*	$3.7 \cdot 10^{-3}$	—	—	—
	—	—	—	7 min	1.38*	$3.5 \cdot 10^{-3}$	—	—	—
	—	—	—	10 min	0.67*	$4.1 \cdot 10^{-3}$	—	—	—
CCl_3COOH	—	—	—	7 min	2.52*	$1.8 \cdot 10^{-3}$	—	—	—
	—	—	—	7 min	2.36*	$2.0 \cdot 10^{-3}$	—	—	—
	—	—	—	10 min	1.71*	$2.0 \cdot 10^{-3}$	—	—	—
	—	—	—	15 min	0.95*	$2.2 \cdot 10^{-3}$	—	—	—
		50°			65°			80°	
CF_3COOH***	5 hr 20 min	4.00	$2.3 \cdot 10^{-5}$	1 hr	2.98*	$1.6 \cdot 10^{-4}$	10 min	3.36*	$7.5 \cdot 10^{-4}$
	5 hr 21 min	4.03	$2.2 \cdot 10^{-5}$	1 hr 20 min	2.84*	$1.3 \cdot 10^{-4}$	10 min	4.03	$7.2 \cdot 10^{-4}$
	5 hr 23 min	4.10	$2.1 \cdot 10^{-5}$	1 hr 30 min	2.75	$1.6 \cdot 10^{-4}$	15 min	3.12	$7.9 \cdot 10^{-4}$
	5 hr 32 min	3.92	$2.3 \cdot 10^{-5}$	1 hr 30 min	2.80	$1.5 \cdot 10^{-4}$	15 min	2.98	$8.4 \cdot 10^{-4}$
	—	—	—	—	—	—	16 min	2.98	$7.9 \cdot 10^{-4}$
	—	—	—	—	—	—	17 min	2.86	$7.9 \cdot 10^{-4}$

* Experiments are marked with an asterisk.

** E = 2.29 Cal/mole; log A = 9.0.

*** E = 26.8 Cal/mole; log A = 13.5.

EXPERIMENTAL

Preparations. The dimethylaniline (Eastman Kodak) was dried over sodium and distilled in vacuum: b.p. 193-193.5°, n_D^{20} 1.5584. The methyldiphenylamine was synthesized by a known method [30] and purified in the same way. The triphenylamine was synthesized by a method described in [31], and was recrystallized twice from alcohol: m.p. 126.5-127°. To introduce deuterium into the ortho-para positions the triphenylamine was dissolved in liquid DBr [24]. p-Deuterodimethylaniline (n_D^{20} 1.5581) and p, p'-dideuteromethyldiphenylamine (n_D^{20} 1.6190) were obtained by the action of D_2O on the lithium derivatives, which were prepared from the corresponding bromides [32-34]. The compounds were carefully purified and diluted with the nondeuterated compounds.

The acetic acid was repeatedly frozen out (m.p. 16.58°). The formic acid was dried with boric anhydride, distilled over boric anhydride in vacuum (in an apparatus with glass filters, which prevented the boric anhydride from falling into the distillate), sealed in ampoules, and kept at 0° (m.p. 8.3°). "Pure" monochloroacetic acid was distilled, the fraction boiling at 187.5-188° (751 mm) was collected, and it was recrystallized from a small amount of benzene (m.p. 63.0-63.5°). The trichloroacetic acid was recrystallized twice from benzene (m.p. 57.5-58.0°). The trichloroacetic acid was obtained by decomposition of the sodium salt; after distillation, m.p. -15.25°. All the operations with the anhydrous acids were carried out in a "dry chamber."

Method of carrying out experiments on deuterium exchange. A weighed sample of the amine (~ 0.25 g) was sealed in a thin-walled small bulb [35] and placed with two glass breakers in a thick-walled ampoule in the neck of which an inlet was made. In a "dry chamber" the ampoule was filled with solvent (50, 100, or 150 moles per mole of amine, depending on the number of rings in the latter*) and closed with a cap ground to fit. The solvent was chilled, the opening in the ground section of the ampoule was lined up with hat in the cap, and the air was evacuated from the ampoule. The ampoule was resealed and placed in a thermostat (accuracy of temperature control was = 0.1-0.15°). After 30 minutes the small bulb with the compound was broken by vigorous shaking of the ampoule and the starting time of the experiment was recorded. At the end of the experiment the ampoule was placed in a cooling mixture and water was added to the solution of the amine in the acid. Triphenylamine was filtered off, washed with water, dissolved in ether, the ether solution was dried with calcium chloride, and the compound was recrystallized twice from anhydrous ethanol and dried. The solutions containing the other amines were neutralized with alkali and the compound was extracted with ether and dried. Finally the amines were distilled in vacuum over pulverized sodium.

A control showed that in the period of the experiments the constants of the compounds did not change and in the course of isolation of the compounds their isotope composition remained constant.

The concentration of deuterium in the compounds was determined by the drop method before the experiment (C_0), at the moment that it ended (C_t), and when equilibrium was attained in the exchange reaction (C_∞). In the process of the exchange reaction with p-deuterodimethylaniline and p,p'-dideuteromethyldiphenylamine, deuterium from the solution entered into the compound as a result of isotope exchange with the ortho hydrogen atoms of the amine. Therefore the values of C_t and C_∞ should be corrected: $C_{\infty(corr.)} = C_\infty/3$; $C_{t(corr.)} = C_t - \Delta C_t$, where ΔC_t changes in relation to t within the limits 0 to $\frac{2}{3} C_\infty$.

$$k = \frac{2.3}{t} \lg \frac{C_0 - C_{\infty\,(corr.)}}{C_{t(corr.)} - C_{\infty\,(corr.)}}.$$

Taking into account the degree of accuracy of our experiments, we used approximate values of the corrections in our calculations.

SUMMARY

1. p-Deuterodimethylaniline, p,p'-dideuteromethyldiphenylamine, and triphenylamine were synthesized, containing deuterium in all ortho-para positions.

2. The rate of exchange of the deuterium in the amines mentioned with anhydrous carboxylic acids (CH_3COOH, $HCOOH$, $CH_2ClCOOH$, CCl_3COOH, CF_3COOH) was measured. It was shown that with increasing strength of the acid (and with an increase in its dielectric constant) the rate decreases and the energy of activation increases for the exchange of the deuterium in the dimethylaniline and the rate of the exchange reaction with triphenylamine increases, but the value of the rate constant for hydrogen exchange with methyldiphenylamine passes through a maximum. The relative order of the rate constant for deuterium exchange in the three amines with acetic acid and with trifluoroacetic acid proved to be diametrically opposite..

* To dissolve triphenylamine in formic acid, 1100-1200 moles of the latter was used per mole of the amine.

TABLE 5. Experiments with Triphenylamine (C_0 = 12.88; C_∞ = 0.65)

Acid	Temperature	t	c_t	k
CH_3COOH	115°	63 hr 30 min	5.52	$4 \cdot 10^{-6}$
	115	67 hr	6.63	$3 \cdot 10^{-6}$
	115	71 hr	6.63	$3 \cdot 10^{-6}$
	115	72 hr	5.76	$3 \cdot 10^{-6}$
	90*	39 hr	0.14	$1.8 \cdot 10^{-7}$
	90	171 hr	0.59	$1.3 \cdot 10^{-7}$
	90	226 hr	0.67	$1.2 \cdot 10^{-7}$
HCOOH**	90	40 min	4.86	$4 \cdot 10^{-4}$
	90	40 min	1.45	$8 \cdot 10^{-4}$
	90	40 min	2.13	$6 \cdot 10^{-4}$
	90	40 min	1.47	$9 \cdot 10^{-4}$
	90	40 min	6.25	$3 \cdot 10^{-4}$
$CH_2ClCOOH$	90	15 min	4.50	$1.3 \cdot 10^{-3}$
	90	15 min	4.15	$1.4 \cdot 10^{-3}$
	90	20 min	3.23	$1.3 \cdot 10^{-3}$
	90	25 min	3.60	$1.0 \cdot 10^{-3}$
	65	2 hr 30 min	4.27	$1.4 \cdot 10^{-4}$
	65	2 hr 30 min	3.91	$1.5 \cdot 10^{-4}$
	65	2 hr 30 min	4.24	$1.4 \cdot 10^{-4}$
CF_3COOH**	30	15 min	4.21	$1.8 \cdot 10^{-3}$
	30	15 min	4.32	$1.7 \cdot 10^{-3}$

* Experiments were carried out with CH_3COOD (concentration of deuterium 12.86 mole-%) and ordinary triphenylamine.

** In experiments with HCOOH $C_\infty \simeq 0$, in experiments with CF_3COOH C_∞ = 1.96.

3. The results obtained can be explained by taking into account the dual reaction capacity of the amines, which depends on the effect of p,π-conjugation, and also the destruction of conjugation when the amines are ionized. The results confirm that Bronsted's scheme is adequate for the description of reactions between all acids and bases, and therefore it is necessary to change their definitions. New definitions have been proposed for acid and base.

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SYNTHESIS OF CIS-1,2-DI(IODOMETHYL)CYCLOBUTANE AND SOME DERIVATIVES OF BICYCLO[3.2.0]HEPTANE

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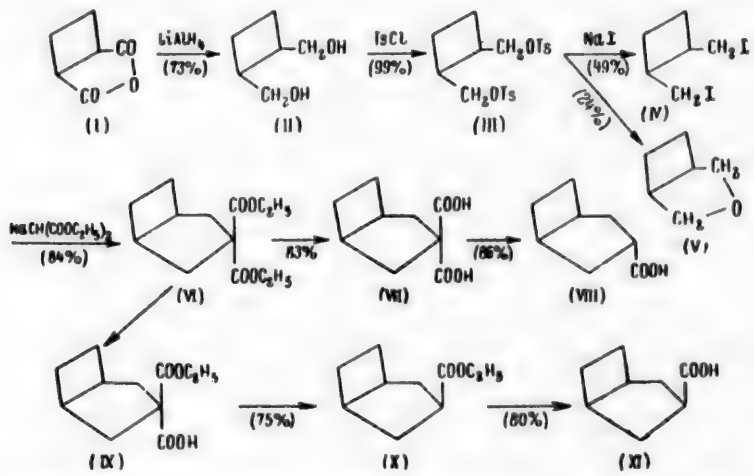
At the present time no disubstituted homolog of cyclobutane with an exactly established configuration is known. Conclusions regarding the spatial arrangement of the substituents in the molecules, for example of 1,2- or 1,3-dimethylcyclobutanes [1,2], and also a number of other compounds genetically related to them, are based exclusively on the Auwers-Skita rule, which is now known [3] to have only limited application.

In order to reach a solution of this problem by a chemical route, in the present work we subjected to reduction with the aid of lithium aluminum hydride, the anhydride of cis-cyclobutanedicarboxylic-1,2 acid (I) and obtained, in accordance with previous indications [4], 1,2-dimethylolcyclobutane (II), which was converted through the ditosylate (III) to the previously undescribed 1,2-di(iodomethyl)cyclobutane (IV). We treated the latter with the sodium derivative of malonic ester, assuming that only the cis-compound could in this case give a derivative of bicyclo[3.2.0]-heptane. As a result we actually obtained the expected diethyl ester of bicyclo[3.2.0]heptanedicarboxylic-3,3 acid (VI), bicyclo[3.2.0]heptanedicarboxylic-3,3 acid (VII), and by decarboxylation of the latter bicyclo[3.2.0]heptanecarboxylic-3 acid, which probably was a mixture of two stereoisomers with a predominance of the more stable exo-form (VIII). Upon partial saponification of the ester (VI) with one mole of caustic alkali, it was converted in 75% yield to the partial ester of bicyclo[3.2.0]heptanedicarboxylic-3,3 acid (IX), which gave on decarboxylation the ethyl ester of bicyclo[3.2.0]heptanecarboxylic-3 acid (X). This indicates the heterodynamic nature of the two carboethoxy groups in the molecule of the ester (VI) and is in agreement with the behavior, for example, of the esters of 1-methylcyclobutanedicarboxylic-2,2 [5] or 1,3-dimethylcyclopentanedicarboxylic-2,2 acid [6], in which the carboethoxy groups also have different activities. The ester (X) formed on saponification is a monocarboxylic acid, although it also appears, if we judge from the constants, that it is a mixture of stereoisomers, but probably contains predominantly the endo-form (XI), since its amide after four recrystallizations had a constant m.p. 162-163°, while the amide of the acid (VIII) melted at 184-185°.



All of the compounds referred to above have not been described until the present work. Their formation shows that the starting glycol (II) and diiodide (IV) actually belong to the cis series. This conclusion is confirmed also by

the formation of 3-oxabicyclo[3.2.0]heptane (V) as a byproduct when sodium iodide acts on the ditosylate (III). This bicyclic ether was formed also when 1,2-dimethylolcyclobutane (II) was distilled in vacuum in the presence of traces of hydrochloric acid, in the same way that 2,2,4,4-tetramethyl-3-oxabicyclo[3.2.0]heptane is produced from cis-1,2-diisopropylolcyclobutane [7].

The results of our experiments are significant in another way, revealing a new route for the synthesis of derivatives of bicyclo[3.2.0]heptane which are difficult to obtain at the present time. Up to now these compounds have been prepared almost exclusively by the reaction of cyclopentadiene with ketenes. Thus, by the addition of the simplest ketene to cyclopentadiene, bicyclo[3.2.0]hepten-2-one-6 has been synthesized in 17-18% yield [8-11]; by the reduction of this compound by Kizhner's method bicyclo[3.2.0]heptene-2 has been obtained, and from the last named compound bicyclo[3.2.0]heptane has been prepared by catalytic hydrogenation [9]. By the reaction of cyclopentadiene with dimethyl- and diphenyl ketenes in a similar manner 7,7-dimethylbicyclo[3.2.0]heptene-2-one-6 [12-14] and 7,7-diphenylbicyclo[3.2.0]hepten-2-one-6 [15,16] were prepared and converted by hydrogenation to the corresponding saturated ketones.

A variation of this method is the reaction of cyclopentadiene with phenylbenzoyldiazomethane [17], which under the reaction conditions is converted first to diphenyl ketene, which reacts further with the cyclopentadiene as described above.

By the addition of tetrafluoroethylene to cyclopentadiene, 6,6,7,7-tetrafluorobicyclo[3.2.0]heptene-2 was obtained [18].

Besides the synthetic methods mentioned above, compounds of the bicyclo[3.2.0]heptene series are produced according to the statements of some authors [19-21], by the oxidation of various derivatives of caryophyllene, but these reactions are not suitable for preparative purposes.

Finally, the compound obtained by photoisomerization of the methyl ether of γ-tropolone [22] apparently is 1-methoxybicyclo[3.2.0]heptadien-2,6-one-4.

In view of the fact that the anhydride of cis-cyclobutanedicarboxylic-1,2 acid is now a comparatively available compound, the experiments described below widen the possibilities of preparing still unknown derivatives of bicyclo[3.2.0]heptane and may facilitate their further study.

EXPERIMENTAL

The starting anhydride of cis-cyclobutanedicarboxylic-1,2 acid (I) was prepared by the method described by us previously [23] and had the b.p. 113-114° (2 mm) and m.p. 78°.

1,2-Dimethylolcyclobutane (II). Reduction of the anhydride (I) was carried out in a round-bottomed flask fitted with a mechanical stirrer and a dropping funnel, which served as an extractor and was connected with a reflux condenser which was protected from moisture by a calcium chloride tube. In the flask was placed a solution of lithium aluminum hydride prepared from 22.4 g of lithium hydride, 188.3 g of aluminum bromide, and 880 ml of absolute ether, and 63 g of the anhydride (I) was placed in the dropping funnel.

The solution of lithium aluminum hydride was boiled on a water bath until all the anhydride was dissolved by the ether draining from the condenser, after which the heating was continued for another 5 hours, and then all was left until the next day.

The excess lithium aluminum hydride was decomposed with 100 ml of ice water and the precipitate which had separated out was almost completely dissolved by the addition of 900 ml of 10% hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with ether in a continuous extractor for 4 days.

The combined ether extracts were washed with a solution of sodium bicarbonate, dried with potassium carbonate, the ether was distilled off, and the residue was distilled in vacuum, boiling almost entirely at 104° (2 mm) [4]. The yield from 12 experiments averaged 42.4 g (73.1%).

d_4^{20} 1.0576, n_D^{25} 1.4736 [4], n_D^{20} 1.4750, MR_D 30.93; calculated 31.22.

Ditosylate of 1,2-dimethylolcyclobutane (III). To a solution of 114 g (0.6 mole) of p-toluenesulfonyl chloride in 575 ml of dry pyridine was added dropwise, with cooling to −10°, 34.8 g (0.3 mole) of the glycol (II). The mixture was kept at a low temperature for another 0.5 hour, then gradually warmed to room temperature and left until the next day, after which 900 ml of hydrochloric acid (1:2) was added to it with cooling, the thick oil that separated

out was extracted with ether, the ether extracts were washed with 5% hydrochloric acid, then with water, and dried with sodium sulfate, after which the ether was distilled off. The weight of the remaining yellowish thick oil averaged 126.5 g (99.4%) and it was not further purified.

Cis-1,2-di(iodomethyl)cyclobutane (IV). To 126.5 g (0.3 mole) of the ditosylate (III), in a flask fitted with a reflux condenser, was added a solution of 108 g (0.72 mole) of sodium iodide in 350 ml of anhydrous acetone. The mixture was heated to boiling on a bath for 6-8 hours, after which the larger part of the acetone was distilled off, water was added to the cooled residue, the heavy oil that separated was removed, the water-acetone layer was extracted with ether, the ether extracts combined with the main mass of the reaction product were washed with a solution of sodium sulfate, then with water, and dried with calcium chloride, after which the solvent was distilled off and the residue was fractionated in vacuum. First an average of 7 g (23.8%) of 3-oxabicyclo[3.2.0]heptane (V) passed over with a b.p. of 44° (55 mm), and then 49.6 g (49.4%) of the diiodide (IV) with a b.p. of 110-111° (2 mm), which quickly crystallized. The product was washed on a funnel with chilled methyl alcohol and the light yellow crystals obtained were used for the subsequent experiments (in further experiments only the 3-oxabicyclo[3.2.0]heptane was distilled; the residue was poured into a dish and the diiodide (IV) that crystallized was separated and washed with chilled methyl alcohol).

The compound was readily soluble in ether and chloroform, difficultly so in methyl or ethyl alcohol. An analytically pure sample was prepared by recrystallization from a mixture of ether and methyl alcohol and formed colorless prismatic crystals with a characteristic odor.

M.p. 34-35°, d_4^{40} 2.1828, n_D^{40} 1.6195, MR_D 54.03; calc. 53.77.

Found %: I 75.32. $C_6H_{10}I_2$ Calculated %: I 75.60

3-Oxabicyclo[3.2.0]heptane was freed of traces of pyridine by washing with 5% hydrochloric acid and with water, drying with calcium chloride, and distilling at 120-121° (760 mm), after which it was a colorless mobile liquid with a strong characteristic odor.

d_4^{20} 0.9558, n_D^{20} 1.4520, MR_D 27.55; calc. 27.61.

Found %: C 73.26; H 10.34. $C_6H_{10}O$. Calculated %: C 23.47; H 10.20.

The compound did not react with bromine in the cold nor with metallic sodium even when boiled.

Bicyclo[3.2.0]heptanedicarboxylic-3,3 acid (VII) and its diethyl ester (VI). To a solution of the alcoholate prepared from 11.5 g of sodium and 175 ml of anhydrous alcohol were added first 80 g of malonic ester, and then gradually 84 g of the diiodide (IV). The mixture was refluxed on a bath until there was complete solution of the diiodide and a neutral reaction to litmus (3 hours), then water was added to it, with cooling, it was acidified with sulfuric acid, the oil that separated was extracted with ether, the ether extracts were washed with a solution of sulfite and with water, dried with calcium chloride, the ether was distilled off, and the residue was fractionated in vacuum. On distillation, 37 g of malonic ester was recovered with b.p. 58-65° (2 mm) and 50.7 g (84.5%) was obtained of a fraction with b.p. 104-105° (2 mm) consisting of the impure ester of bicyclo[3.2.0]heptanedicarboxylic-3,3 acid (VI), which we were unable to free of contaminants by further distillations in vacuum. Therefore 10 g (0.04 mole) of the ester (VI) obtained was saponified with a solution of 7 g (0.125 mole) of potassium hydroxide in 70 ml of alcohol. After the usual treatment, 6.4 g (83.6%) of a crystalline acid was obtained with m.p. 180-181° (from a mixture of ether and benzene).

Found %: C 58.75; H 6.61. $C_9H_{12}O_4$. Calculated %: C 58.69; H 6.52.

A 7.4-gram (0.04 mole) sample of the pure dicarboxylic acid (VII) was converted by means of thionyl chloride to the dichloride of the acid and further to the starting diethyl ester (VI).

B.p. 103-104° (2 mm) d_4^{20} 1.0669, n_D^{20} 1.4560, MR_D 61.24; calc. 61.60.

Found %: C 64.87; H 8.41. $C_{13}H_{20}O_4$. Calculated %: C 65.00; H 8.33.

Ethyl ester of bicyclo[3.2.0]heptanecarboxylic-3 acid (X). Fifty grams (0.21 mole) of the ester (VI) was saponified with a solution of 14 g (0.25 mole) of potassium hydroxide in 140 ml of alcohol for 4 hours. After addition of water and distillation of the alcohol, the alkaline liquid was extracted with ether and 5.4 g of unsaponified ester (VI) was recovered. The crude partial ester (IX) that separated out upon subsequent acidification with sulfuric acid was

extracted with ether and after drying of the ether extract with sodium sulfate and removal of the solvent was decarboxylated by heating on an oil bath to 215°. The residue was treated in ether solution with alkali in order to extract the free acid, of which 3.3 g (12.7%) was obtained. The remaining ether solution was washed with water, dried with calcium chloride, the solvent was distilled off, and the residue was distilled in vacuum; yield 23.3 g (74.9%).

B.p. 104.5-105° (18 mm), d_4^{20} 1.0013, n_D^{20} 1.4570, MR_D 45.70; calc. 46.09.

Found %: C 71.56; H 9.71. $C_{10}H_{16}O_2$. Calculated %: C 71.43; H 9.52.

Bicyclo[3.2.0]heptanecarboxylic-3 acid (VIII) and (XI). A 21-gram sample (0.125 mole) of the ester (X) was saponified with 10% alcoholic solution of potassium hydroxide and the monocarboxylic acid obtained after the usual treatment was distilled in vacuum, whereupon almost all distilled within the range 105-106° (3 mm). Yield 14 g (80%).

d_4^{20} 1.0917, n_D^{20} 1.4800, MR_D 36.41; calc. 36.74.

Found %: C 68.37; H 8.71. $C_8H_{12}O_2$. Calculated %: C 68.57; H 8.57.

Three grams of the acid was converted by the action of thionyl chloride to the acid chloride, which without further purification was treated in ether solution with dry ammonia. From the mixture obtained the amide was extracted with chloroform and recrystallized 4 times from the same solvent, after which it formed colorless, fine needles with m.p. 162-163°.

Found %: N 9.88. $C_8H_{13}ON$. Calculated %: N 10.07.

In another experiment 7.9 g of the dicarboxylic acid (VII) was decarboxylated by heating on an oil bath to 190° for 0.5 hour. The monocarboxylic acid remaining in the flask boiled on vacuum distillation at 105-106° (3 mm), 5.2 g (86.3%).

d_4^{20} 1.0899, n_D^{20} 1.4800, MR_D 36.49; calc. 36.74.

Found %: C 68.42; H 8.68. $C_8H_{12}O_2$. Calculated %: C 68.57; H 8.57.

The amide of bicyclo[3.2.0]heptanecarboxylic-3 acid (VIII) obtained in the above-described manner melted at 184-185° (from chloroform).

Found %: N 10.02. $C_8H_{13}ON$. Calculated %: N 10.07.

SUMMARY

1. By the action of sodium iodide in acetone on the ditosylate of 1,2-dimethylolcyclobutane, the previously undescribed 1,2-di(iodomethyl)cyclobutane was prepared.

2. By the action of the sodium derivative of malonic ester on 1,2-di(iodomethyl)cyclobutane a number of new derivatives of bicyclo[3.2.0]heptane were obtained.

3. The production under the conditions mentioned of derivatives of bicyclo[3.2.0]heptane demonstrates that 1,2-di(iodomethyl)cyclobutane and 1,2-dimethylolcyclobutane are cis-compounds.

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INVESTIGATION IN THE FURANE SERIES

XVI. N-(β-HYDROXYETHYL)FURFURYLAMINES IN THE SYNTHESIS OF PIPERAZINES AND ETHYLENE DIAMINES CONTAINING THE FURANE RING

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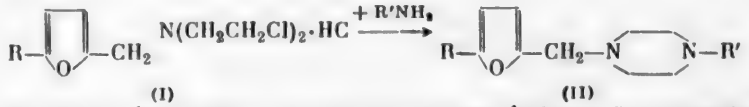
Some substituted ethylenediamines [1,2] and also unsymmetrically N,N'-substituted piperazines (in contrast to the symmetrical compounds) are physiologically active [3] and find practical use. Similar systems containing a furane ring, however, are almost undescribed in the literature. In connection with this, since we had developed a convenient method for the synthesis of mono- and dihydroxyalkylfurfurylamines, and from them the β-chloroalkylfurfurylamines [4,5], it was of interest to carry out on this basis the synthesis of ethyleneamines and piperazines having a furane ring in their makeup.

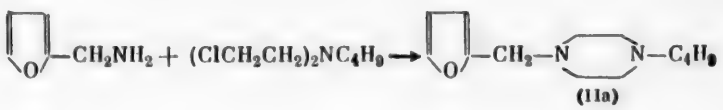
By the reaction of primary amines with the hydrochlorides of di[N-(β-chloroethyl)]furfurylamines (Ia, b) we prepared the corresponding N-furfurylpiperazines (IIa-d), but the reaction was accompanied by considerable decomposition, as a result of which the yields of the furfurylpiperazines were 25-40 %.



(I) (II)

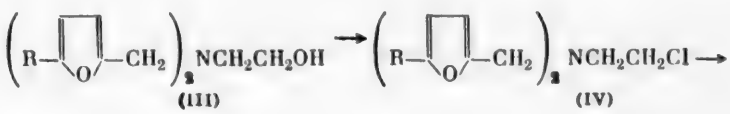
(I) a) R = H, b) R = CH_3; (II) a) R = H, R' = C_4H_9, b) R = H, R' = $(C_4H_3O)CH_3$; c) R = H, R' = C_6H_5, d) R = CH_3, R' = $CH_2(C_4H_3O)CH_3$.

Compounds of this type also can be prepared by the reaction of 2-furfurylamine with di(β-chloroalkyl)alkylamines; thus, N-butyl-N'-furfurylpiperazine (IIa) was prepared by us by the reaction of di(β-chloroethyl)butylamine and furfurylamine.

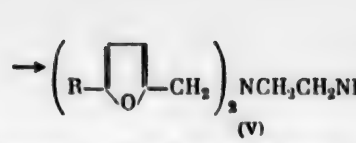


(IIa)

To prepare ethylenediamines with two furfuryl radicals on one nitrogen atom, we converted the N-(β-hydroxyethyl)difurfurylamines (IIIa, b) to the hydrochlorides of the corresponding N-(β-chloroethyl)difurfurylamines (IVa, b) and reacting them with secondary amines, obtained the unsymmetrically substituted ethylene diamines (Va, b, c) with ethyl or pentamethylene radicals on the other nitrogen atom.



(III) (IV)



(V)

(III) a) R = H, b) R = CH_3; (IV) a) R = H, b) R = CH_3; (V) a) R = H, R′ = C_2H_5, b) R = H, R_2' = $(CH_3)_2$, c) R = CH_3, R_2' = $(CH_3)_2$.

EXPERIMENTAL

I. Synthesis of N-furfurylpiperazines

N-Butyl-N′-furfurylpiperazine (IIa). a) To a solution of 20 g of the hydrochloride of N,N-di(β-chloroethyl)furfurylamine (Ia) [5] in 30 ml of anhydrous alcohol was added, during 40 minutes, with stirring, a solution of 11 g of butylamine in 15 ml of alcohol, after which the mixture was boiled for 15 hours, evaporated in vacuum, and the residue was treated with an excess of 40% potassium hydroxide solution. The organic layer, combined with the ether extracts from the aqueous alkali layer, was dried with potassium carbonate. After the ether and the unchanged butylamine had been distilled off, the residue was distilled in vacuum. Yield 4.5 g (25%).

B.p. 97-98° (2 mm), n_D^{20} 1.4878, d_4^{20} 0.9694, MR_D 66.05. $C_{13}H_{22}ON_2F_2$. Calculated: 66.42

Found %: C 70.06, 69.54; H 10.18, 9.99. $C_{13}H_{22}ON_2$. Calculated %: C 69.78; H 9.97.

Dipicrate: decomp. temp. 215-218° (from acetone).

Found %: C 43.99, 44.26; H 4.30, 4.28; N 16.20, 16.25. $C_{25}H_{28}O_{15}N_8$. Calculated %: C 44.12; H 4.14; N 16.47.

b) From 6 g of N,N-di(β-chloroethyl)butylamine and 4.3 g of furfurylamine, as described above, we obtained 0.8 g (14.5%).

B.p. 97-98° (2 mm). Dipicrate: decomp. temp. 214-218°. A mixed sample with the dipicrate described above gave no perceptible depression in melting point.

N,N′-Difurfurylpiperazine (IIb). a) From 20 g of (Ia) and 15.1 g of furfurylamine, as described above, 3 g (15%) were obtained.

B.p. 138-141° (2 mm); m.p. 55° (from petroleum ether).

Found %: C 68.41, 68.42; H 7.48, 7.45. $C_{14}H_{18}O_2N_2$. Calculated %: C 68.27; H 7.37.

Dipicrate: decomp. temp. 235-239° (from alcohol).

Found %: C 44.84, 44.78; H 3.70, 3.69. $C_{26}H_{24}O_{16}N_8$. Calculated %: C 44.33; H 3.43.

b) From 15.8 g of ethylene dibromide and 8.2 g of furfurylamine, as described above, we obtained 1 g (5%).

B.p. 138-141° (2 mm). Dipicrate: decomp. temp. 234-239°; a mixed sample with the dipicrate from the preceding experiment gave no perceptible depression in melting point; decomp. temp. 235-239°.

N-Furfuryl-N′-phenylpiperazine (IIc). To a solution of 8.5 g of (Ia) in 25 ml of anhydrous alcohol was added an alcoholic solution of 6.8 g of aniline, the mixture was boiled for 3 hours and left for 12 hours. Yield 4.5 g (46%) of hydrochloride of (IIc): decomp. temp. 204-207° (from alcohol).

Found %: C 64.91, 65.03; H 6.91, 6.97. $C_{15}H_{19}ON_2Cl$. Calculated %: C 64.63; H 6.87.

By treatment of the hydrochloride with a solution of sodium carbonate and subsequent extraction with ether, we isolated the free base; m.p. 49-50° (from ether).

Found %: C 74.22, 74.15; H 7.49, 7.57; N 11.26, 11.29. $C_{15}H_{18}ON_2$. Calculated %: C 74.35; H 7.49, N 11.56.

N,N′-Di(5-methylfurfuryl)piperazine (IId). To a solution of 7.3 g of the hydrochloride of N,N-di(β-chloroethyl)-5-methylfurfurylamine (Ib) in 25 ml of anhydrous alcohol was added an alcoholic solution of 5.7 g of 5-methylfurfurylamine. The mixture was refluxed for 3 hours and left for 12 hours. Yield 3.1 g (32.5%) of dihydrochloride of (IId) decomp. temp. 260-264° (from aqueous acetone).

Found %: C 55.22, 55.33; H 7.04, 6.99; N 8.33, 8.35. $C_{15}H_{24}O_2N_2Cl_2$. Calculated %: C 55.33; H 6.96; N 8.07.

The base isolated from the hydrochloride melted at 55.5-56° (from ether).

Found %: C 70.48, 70.47; H 7.93, 8.08; N 10.10, 10.06. $C_{15}H_{22}O_2N_2$. Calculated %: C 70.04; H 8.08; N 10.24.

II. Synthesis of N,N-difurfurylethylenediamines.

N,N-Diethyl-N', N'-difurfurylethylenediamine (Va). To 25 g of diethylamine in 25 ml of anhydrous alcohol was added dropwise 40 g of the hydrochloride of N-(β-chloroethyl)difurfurylamine (IVa) in 40 ml of anhydrous alcohol. Then 10 g of finely ground potassium carbonate was added and the mixture was boiled for 5 hours. The precipitate was removed and the filtrate was made alkaline with a concentrated aqueous solution of potassium hydroxide. The organic layer, combined with the ether extracts from the aqueous layer, was dried with potassium carbonate. The ether was distilled off and the residue was distilled in vacuum. Yield 13.7 g (35.5%).

B.p. 132-135° (4 mm), n_D^{20} 1.4990, d_4^{20} 1.0189, MR_D 79.64. $C_{15}H_{24}O_2N_2F_4$. Calculated: 80.98.

Found %: C 69.15, 68.96; H 8.91, 8.73; N 10.12, 9.97. $C_{15}H_{24}O_2N_2$. Calculated %: C 69.53; H 8.75; N 10.13.

Dipicrate: m.p. 145° (from alcohol).

Found %: N 15.12, 15.04. $C_{29}H_{30}O_{16}N_8$. Calculated %: N 15.25.

N,N-Difurfuryl-N',N'-pentamethylenethylenediamine (Vb). From 3.7 g of (IVa) and 2.5 g of piperidine, as described above, we obtained 2.2 g (59%).

B.p. 185-187° (5 mm), n_D^{20} 1.5185, d_4^{20} 1.0634, MR_D 82.24. $C_{17}H_{24}O_2N_2F_4$. Calculated: 83.40.

Found %: C 71.04, 70.79; H 8.38, 8.24; N 9.33, 9.49. $C_{17}H_{24}O_2N_2$. Calculated %: C 70.80; H 8.38; N 9.71.

N,N-Di(5-methylfurfuryl-2)-N',N'-pentamethylenethylenediamine (Vc). A mixture of 13.2 g of di(5-methylfurfuryl) amine [2], 5.6 g of ethylene oxide, and several drops of water were allowed to stand for a day. Upon distillation in vacuum, 11.7 g (73%) of N-(β-hydroxyethyl)di(5-methylfurfuryl)amine (IIIb) was obtained.

B.p. 145-146.5° (2 mm), n_D^{20} 1.5150, d_4^{20} 1.0973, MR_D 68.51. $C_{14}H_{19}O_3NF_4$. Calculated: 69.33.

Found %: C 67.16, 67.17; H 7.77, 7.91. $C_{14}H_{19}O_3N$. Calculated %: C 67.45; H 7.68.

To 7 g of (IIIb) in 20 ml of chloroform was added a solution of 2.3 ml of thionyl chloride in 15 ml of chloroform. After the solvent had been distilled off, the hydrochloride of N-(β-chloroethyl)di(5-methylfurfuryl)amine, which was obtained in the form of a noncrystallizing oil, was treated with 6.2 g of piperidine and 40 ml of anhydrous alcohol. The mixture was heated for 5 hours and treated as described above. Upon distillation of the reaction product in vacuum, we obtained 2.5 g (28%) of (Vc).

B.p. 142-144° (2 mm), n_D^{20} 1.5150, d_4^{20} 1.0391, MR_D 91.83. $C_{19}H_{28}O_2N_2F_4$. Calculated: 92.64.

Found %: C 72.12, 72.14; H 8.95, 8.86. $C_{19}H_{28}O_2N_2$. Calculated %: C 72.12; H 8.92.

Dipicrate: m.p. 145° (from alcohol).

Found %: N 14.06, 13.97. $C_{31}H_{34}O_{16}N_8$. Calculated %: N 14.47.

N-(β-Chloroethyl)di(5-methylfurfuryl-2)amine. The hydrochloride of (IVb) prepared from 14.5 g of (IIIb) and 4.9 g of thionyl chloride was treated with a saturated solution of sodium carbonate. The organic layer, combined with the ether extracts from the aqueous layer, was dried with magnesium sulfate. After the ether had been distilled off, the residue was distilled in vacuum. Yield 7.1 g (46%).

B.p. 136-137° (1 mm), n_D^{20} 1.5130, d_4^{20} 1.1073, MR_D 72.67. $C_{14}H_{18}O_2NClF_4$. Calculated: 72.67.

Found %: C 62.54, 62.47; H 6.71, 6.69; N 5.08, 4.87. $C_{14}H_{18}O_2NCl$. Calculated %: C 62.80; H 6.77; N 5.23.

Picrate: m.p. 120-121° (from acetone).

Found %: C 48.29, 48.16; H 4.34, 4.35. $C_{20}H_{21}O_9N_4Cl$. Calculated %: C 48.34; H 4.26.

SUMMARY

The reaction of N,N-di(β-chloroethyl)furfurylamines with primary amines and of N-(β-chloroethyl)difurfurylamines with secondary amines is a method of synthesizing piperazines and the corresponding ethyleneamines containing furfuryl substituents.

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CHEMISTRY OF SELENOPHENE

XXXII. β-DIKETONES OF THE SELENOPHENE SERIES

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In one of the preceding communications [1] we described the synthesis of α- and β-ketonoaldehydes of the selenophene series. The present work is devoted to the preparation of β-diketones of this series by reacting 2-acetoselenophene with esters of the acids—acetic, trifluoroacetic, benzoic, furan-2-carboxylic, thiophene-2-carboxylic, and selenophene-2-carboxylic.

R = CH_3, CF_3, C_6H_5, C_4H_3O, C_4H_3S, C_4H_3Se.
R' = C_2H_5, C_3H_7, C_4H_9, CH_3, CH_3, CH_3.

Synthesis of this type of β-diketone, having, on the one hand, a selenienyl-2-radical, and on the other, a methyl, trifluoromethyl, phenyl, furyl-2, thienyl-2, or even a selenienyl-2, is of interest both in elucidating the effect of these groups, different in nature, on the ability of the ketones to form complexes with metals, and also in comparing them in this respect with such adequately studied β-diketones as acetylacetone, benzoylacetone, trifluorothenoylacetone. In one of the foregoing works touching on this question it was shown in the case of selenoyl-2-acetone [2] that as a reagent for extracting thorium from aqueous solutions it was much better than acetylacetone, which is widely used for this purpose.

The character of the spectral absorption curves in the ultraviolet region obtained by us for β-ketones of the selenophene series (Figs. 1 and 2) is in the main similar to the character of the u.v.-spectral curves for such similarly composed β-diketones as benzoylacetone (λ_{max} 244-245 and 310 mμ) and dibenzoylmethane (λ_{max} 250 and 345 mμ) [3]. However, as seen from the data given in the table, presence of a selenienyl radical in the β-diketone molecule, and also successive substitution of the alkyl radical in β-diketones of this series by phenyl, furyl, thienyl, or selenienyl causes a displacement of the absorption maximum toward the longer-wave region.

When reacted with cupric acetate, the β-diketones prepared by us readily form intracomplex Cu^{++} compounds. Their u.v.-absorption spectra (taken in chloroform) are similar as regard character of the curves to the absorption spectra of the β-diketones themselves, since they also have two well-defined absorption maxima and, in addition, an area in the ~610-670 mμ region (Figs. 3 and 4), which is characteristic for β-diketone Cu^{++}-complexes. λ_{max} and log ε for these u.v.-spectra are given in the table.

EXPERIMENTAL

ω-Acetyl-2-acetoselenophene (acetylselenenoyl-2-methane). To a three-necked flask with stirrer, reflux condenser, and dropping funnel, containing sodium amide, prepared from 8.6 g of sodium [4], in 300 ml of absolute ether at 20° and with stirring was added 30 g of 2-acetoselenophene in 25 ml of absolute ether, and then 40 g of ethyl acetate in 40 ml of absolute ether. The mixture was stirred for 15 minutes at 20°, for 3 hours with heating on a water bath, cooled, decomposed with a mixture of about 400 g of ice and 90 ml of concentrated hydrochloric acid, extracted with ether and the ethereal extracts dried with magnesium sulfate. After evaporation of ether the residue was distilled in vacuo in a stream of nitrogen. 20 g (71%) of a viscous, straw-yellow oil was obtained, distilling at 146-146.5° (6 mm) and crystallizing in the receiver; m.p. 33-33.5° (from alcohol).

U.v.-Spectra of β-Diketones of the Selenophene Series and Their Intracomplex Cu^{++} Compounds

R	λ_{max} (in mμ)		lg ε	
	$(C_4H_3Se)-COCH_2COR$			
CH_3	277	325	4.24	4.48
CF_3	277	320	4.04	3.80
C_6H_5	247, 285	360	4.15, 4.20	4.76
C_4H_3O	277	372	4.33	4.77
C_4H_3S	278	382	4.06	4.40
C_4H_3Se	280	385	4.09	4.40
	$(C_4H_3Se)-C(=O)-CH=C(-O-)-R$ $Cu/2$			
CH_3	285	345	4.32	4.56
CF_3	302	350	4.02	4.20
C_6H_5	297	355	4.47	4.66
C_4H_3O	307	380	4.33	4.57
C_4H_3S	295	385	4.11	4.28
C_4H_3Se	301	385	3.22	4.47

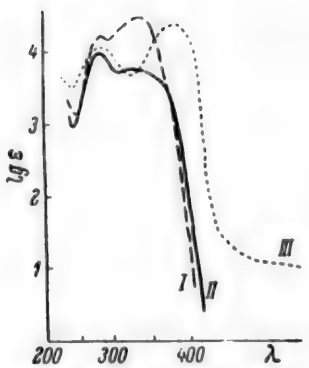

Fig. 1. U.v.-spectra of β-diketones. I) ω-acetyl-2-acetoselenophene; II) ω-trifluoroacetyl-2-acetoselenophene; III) ω-(thenoyl-2'-)-2-acetoselenophene.

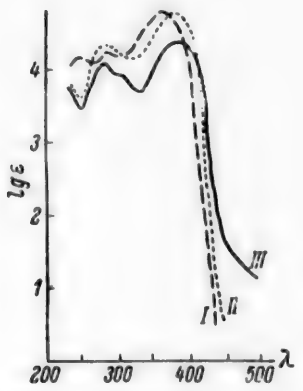

Fig. 2. U.v.-spectra of β-diketones. I) ω-benzoyl-2-acetoselenophene; II) ω-(furoyl-2'-)-2-acetoselenophene; III) ω-(selenenoyl-2')-2-acetoselenophene.

Found %: C 44.81, 44.77; H 3.87, 3.80; Se 31.86, 31.71. $C_8H_8O_2Se$. Calculated %: C 44.67; H 3.75; Se 32.06.

Complex with Cu^{++}. On reacting a saturated alcoholic solution of 0.2 g of diketone and a saturated aqueous solution of cupric acetate, 0.2 g (80%) was obtained; m.p. 205-206° (from alcohol)—dark-green crystals.

Found %: C 38.60, 38.86; H 2.98, 2.75; Se 31.81, 31.74. $C_8H_7O_2SeCu/_2$. Calculated %: C 39.08; H 2.87; S 32.11.

ω-(Trifluoroacetyl)-2-acetoselenophene (trifluoroacetylselenenoyl-2-methane). From 7.5 g of 2-acetoselenophene and 12.4 g of ethyl trifluoroacetate [b.p. 62° (760 mm), n_D^{20} 1.3085] [5] 9.2 g (80%) was obtained as described above; b.p. 118-119° (11 mm), m.p. 32-33° (from methanol)—light-yellow crystals.

Found %: C 36.24, 36.32; H 1.87, 1.91; F 20.73, 20.67. $C_8H_5O_2SeF_3$. Calculated %: C 35.68; H 1.87; F 21.18.

Complex with Cu^{++}. From 0.13 g of diketone and cupric acetate 0.1 g (66%) was obtained as described above; m.p. 236-237° (from methanol)—brilliant rich-green crystals.

Found %: C 31.99, 31.98; H 1.27, 1.29; F 19.40, 19.77. $C_8H_4O_2SeCu/_2F_3$. Calculated %: C 32.0; H 1.35; F 19.00.

ω-Benzoyl-2-acetoselenophene [benzoyl(selenoyl-2)methane]. From 15 g of 2-acetoselenophene and 26 g of ethyl benzoate 17.5 g (74.5%) was obtained as described above; b.p. 226-227° (6 mm), m.p. 65-66° (from methanol)—yellow crystals.

Found %: C 56.60, 56.82; H 3.45, 3.64; Se 28.12, 27.94. $C_{13}H_{10}O_2Se$. Calculated %: C 56.33; H 3.63; Se 28.49.

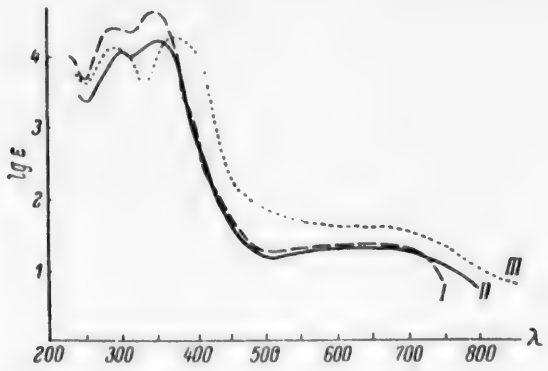

Fig. 3. U.v.-spectra of β-diketone Cu^{++}-complexes. I) Cu-complex of ω-acetyl-2-acetoselenophene; II) Cu-complex of ω-trifluoroacetyl-2-acetoselenophene; III) Cu-complex of ω-(thenoyl-2')-2-acetoselenophene.

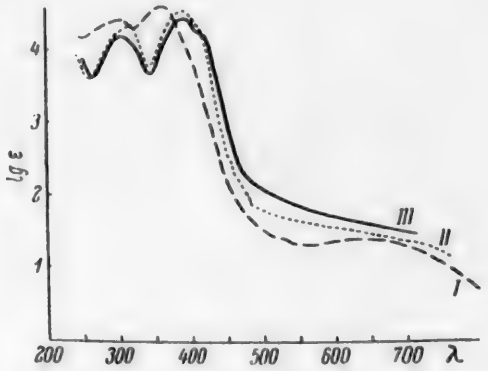

Fig. 4. U.v.-spectra of β-diketone Cu^{++}-complexes. I) Cu-complex of ω-(furoyl-2')-2-acetoselenophene; II) Cu-complex of ω-benzoyl-2-acetoselenophene; III) Cu-complex of ω-(selenenoyl-2')-2-acetoselenophene.

Complex with Cu^{++}. From 0.14 g of diketone and cupric acetate 0.12 g (80%) was obtained; m.p. 267-268° (with decomp.)—yellow-green crystals.

Found %: C 51.09, 50.89; H 3.18, 3.24; Se 25.29, 25.40. $C_{13}H_9O_2SeCu/_2$. Calculated %: C 50.61; H 2.94; Se 25.65.

ω-(Furoyl-2')-2-acetoselenophene [furoyl-2-(selenenoyl-2)methane]. From 7.5 g of 2-acetoselenophene and 10.8 g of methyl pyromucate 8 g (70%) was obtained as described above; b.p. 206-207° (7 mm); m.p. 43-44° (from methanol)—yellow crystals.

Found %: C 49.69, 49.80; H 3.26, 3.11; Se 29.29, 29.18. $C_{11}H_8O_3Se$. Calculated %: C 49.45; H 3.01; Se 29.56.

Complex with Cu^{++}. From 0.13 g of diketone by reacting with cupric acetate 0.11 g (79%) was obtained; m.p. 255-256° (with decomp.)—yellow-green crystals.

Found %: C 43.97, 43.90; H 2.35, 2.21; Se 26.15, 26.25. $C_{11}H_7O_3SeCu/_2$. Calculated %: C 44.34; H 2.36; Se 26.47.

ω-(Thenoyl-2')-2-acetoselenophene [thenoyl-2-(selenoyl-2)methane]. From 7.5 g of 2-acetoselenophene and 12 g of methyl thiophene-2-carboxylate 8.3 g (68%) was obtained as described above; m.p. 91-92° (from methanol)—yellow crystals.

Found %: C 46.40, 46.19; H 3.30, 3.09; Se 27.50, 27.42. $C_{11}H_8O_2SSe$. Calculated %: C 46.72; H 2.84; Se 27.88.

Complex with Cu^{++}. From 0.14 g of diketone by reacting with cupric acetate 0.12 g (75%) was obtained; m.p. 227-228° (with decomp.)—green crystals.

Found %: C 41.74, 41.83; H 2.02, 1.94; Se 24.80, 24.71. $C_{11}H_7O_2SSeCu/_2$. Calculated %: C 42.08; H 2.24; Se 25.15.

ω-(Selenenoyl-2)-2'-acetoselenophene [di(selenenoyl-2)methane]. From 7.5 g of 2-acetoselenophene and 16 g of methyl selenophene-2-carboxylate 10.8 g (72%) was obtained as described above; m.p. 107-108° (from methanol)—yellow crystals.

Found %: C 40.27, 40.32; H 2.50, 2.71; Se 47.51, 47.36. $C_{11}H_8O_2Se_2$. Calculated %: C 40.02; H 2.44; Se 47.84.

Complex with Cu^{++}. From 0.17 g of diketone by reacting with cupric acetate 0.14 g (79%) was obtained; m.p. 259-260° (with decomp.)—green crystals.

Found %: C 36.70, 36.95; H 2.06, 2.20; Se 43.46, 43.32. $C_{11}H_7O_2Se_2Cu/_2$. Calculated %: C 36.65; H 1.95; Se 43.76.

SUMMARY

Condensation of 2-acetoselenophene with esters of acetic, trifluoroacetic, benzoic, furan-2-, and thiophene-2-carboxylic acids leads to preparation of unsymmetric β-diketones, which contain, together with a selenophene ring, a methyl, trifluoromethyl, phenyl, furyl, or thienyl radical; condensation with selenophene-2-carboxylic led to symmetric di(selenenoyl-2)methane.

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INVESTIGATION IN THE FIELD OF ANTIBIOTIC PRECURSOR AND FRAGMENT SYNTHESIS

IV. THIOGLYCOLIC ACID DERIVATIVES

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In the literature, a considerable number thioglycolic acid derivatives are described, prepared as precursors in penicillin biosynthesis. Many unsymmetric sulfides appear to be effective substances; their use in fermentation led to preparation of highly active antibiotics: propyl-, butyl-, allyl-, phenyl-mercaptopenicillins and others [1].

With the aim of studying the biosynthesis of new penicillins and explaining the connection between their structure and biological properties, a series of possible precursors was synthesized – derivatives of propyl- and ethylmercaptoacetic acids differing in the presence and position of functional groups. From propylmercaptoacetic acid derivatives, compounds of general formula $RCH_2R'CHCH_2SCH_2CO_2R''$, where:

R = Br, R' = H, R'' = C_2H_5 (I); R = $OCOCH_3$, R' = H, R'' = C_2H_5 (II); R = OH, R' = H, R'' = C_2H_5 (III); R = H, R' = OH, R'' = C_2H_5 (IV); R = OH, R' = OH, R'' = C_2H_5 (V); R = NH_2, R' = H, R'' = H (VI); R = $NHCOC_6H_5$, R' = H, R'' = H (VIII); sulfone (IX); R = $N(CH_3)_2$, R' = H, R'' = C_2H_5 (XI); R = NO_2, R' = H, R'' = C_2H_5 (XII); R = $C_2H_5O_2CCH_2S$; R' = H, R'' = = C_2H_5 (XIII).

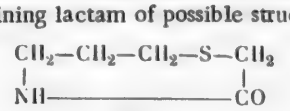
From ethylmercaptoacetic acid derivatives of general formula $RR'CHCH_2SCH_2CO_2R''$ were synthesized compounds, where:

R = $CO_2C_2H_5$, R' = H, R'' = C_2H_5 (XIV); R = CH, R' = H, R'' = C_2H_5 (XV) and R = CO_2H, R' = NH_2, R'' = H (XVI).

Compounds (I), (IV), (V), (XI), (XIII), and (XIV) were prepared by condensing the corresponding halogen-containing derivatives with the thioglycolic ester in an anhydrous alcoholic medium, in presence of an equimolecular amount of sodium alcoholate. Compound (I) was also synthesized in a different manner: by adding gaseous hydrogen bromide to ethyl allylmercaptoacetate. Compound (II) was prepared by acetylating (I); on saponification of (II) and subsequent esterification (III) was prepared. Amino acid (VI) was synthesized by condensing 1-amino-3-bromopropane with thioglycolic acid in aqueous alkaline solution. From (VI) were prepared: hydrochloride (VII), N-benzoyl derivative (VIII), and sulfone (IX).

In experiments to prepare the ethyl ester of amino acid (VI) by heating with anhydrous ethyl alcohol in presence of catalytic amounts of sulfuric acid, instead of the expected amino acid ester of composition $C_7H_{15}O_2NS$ a crystalline substance of nonbasic character was obtained, insoluble in acid, of composition C_5H_9ONS (X). On reacting 1-amino-3-bromopropane with ethyl thioglycolate in presence of sodium alcoholate, substance (X) was also obtained. On heating the latter with concentrated hydrochloric acid the hydrochloride was obtained (VII).

The results obtained afford the possibility of proposing that the ester of amino acid (VI) is very unstable, and is readily cyclized, forming a sulfur-containing lactam of possible structure (X).



(X)

Initial halogen derivative	Substance synthesized	Boiling point (pressure in mm)	Yield (%)	Molecular formula	Found (%)	Calculated (%)
$BrCH_2CH_2CH_2Br$ [5]	$BrCH_2CH_2CH_2SCH_2CO_2C_2H_5$ (I)	107—108° (3)	59	$C_7H_{13}O_2SBr$	C 34.88, H 5.66	C 34.85, H 5.39
$CH_3CHOHCH_2Br$ [6]	$CH_3CHOHCH_2SCH_2CO_2C_2H_5$ (IV)	105—107 (4)	60	$C_7H_{14}O_3S$	C 47.12, H 8.06, S 18.0J	C 47.19, H 7.86, S 17.97
$ClH_2OHCHOHCH_2Cl$ [7]	$CH_2OHCHOHCH_2SCH_2CO_2C_2H_5$ (V)	180—181 (7)	40	$C_7H_{14}O_4S$	C 43.01, H 6.99	C 43.29, H 7.21
$(CH_3)_2NCHCH_2CH_2Cl$ [8]	$(CH_3)_2NCHCH_2CH_2SCH_2CO_2C_2H_5$ (XI)	100—105 (5)	80	$C_9H_{19}O_2SN$	C 52.89, H 9.57, S 15.38, N 6.86	C 52.68, H 9.26, S 15.60, N 6.82
$BrCH_2CH_2CH_2Br$ [5]	$SCH_2CH_2CH_2—S$ $CH_2CO_2C_2H_5$ $CH_2CO_2C_2H_5$ (XIII)	168—170 (3)	20*	$C_{11}H_{20}O_4S_2$	C 46.98, H 7.38, S 22.28	C 47.14, H 7.14, S 22.85
$C_2H_5OCOCH_2CH_2Br$ [9]	$C_2H_5OCOCH_2CH_2SCH_2CO_2C_2H_5$ (XIV)	139—140 (5)	75	$C_9H_{16}O_4S$	C 49.34, H 7.52, S 14.40	C 49.09, H 7.27, S 14.54

*Obtained as a reaction by-product in synthesis of (I).

Nitro derivative (XII) was synthesized from nitroallyl and the thioglycolic ester under the conditions described for preparation of the nitrile (XV) [2]. The cysteineacetic acid (XVI) was prepared from cysteine and chloroacetic acid [3].

The mercaptoacetic acid derivatives synthesized by us were studied as precursors in penicillin biosynthesis. In this regard it was established that substances (II-VI), (VIII), (IX), (XI), and (XIII-XV), introduced into the cultural medium during fermentation of the fungus Penicillium chrysogenym, lead to formation of new, biologically active penicillins with antibacterial activity different from penicillin "g."

EXPERIMENTAL

Ethyl esters of γ-bromopropylmercaptoacetic acid (I), γ-hydroxypropylmercaptoacetic acid (IV), β, γ-dihydroxypropylmercaptoacetic acid (V), N-dimethylaminopropylmercaptoacetic acid (XI), diethyl esters of trimethylene-1,3-dimercaptoacetic acid (XIII) and N-carboxyethylmercaptoacetic acid (XIV) were prepared by one general method: to sodium alcoholate, prepared from 1.15 g of Na and 40 ml of anhydrous alcohol, was added with stirring and cooling (4-5°) a solution of 6 g (0.05 mole) of ethyl thioglycolate in 50 ml of anhydrous alcohol. To the resulting ethyl Na-mercaptoacetate was added dropwise over a period of 40-45 minutes the corresponding halogen derivative following which the reaction solution was heated to boiling, this temperature being maintained for 3-4 hours. After removal of alcohol in vacuo, to the cooled semicrystalline residue were added 10-15 ml of water and 40-50 ml of ether; the upper ethereal layer, containing the mercaptoacetic acid derivative, was dried and concentrated by evaporation, and the residue distilled in vacuo (see table). Compound (I) was also synthesized by another method: into a solution of ethyl allylmercaptoacetate [1] (16 g) in glacial acetic acid (10 ml) cooled to -10° was bubbled dry gaseous HBr until increase in weight of the reaction solution ceased. After removal of excess HBr in vacuo (70-80 mm) at room temperature, the residue was dissolved in ether (100 ml), the ethereal solution carefully washed with 10% soda, water, dried, concentrated, and the residue distilled at 102-108° (3 mm). Yield 58%.

Ethyl ester of γ-acetoxypropylmercaptoacetic acid (II). 9.5 g of (I) was boiled for 2 hours with freshly prepared fused potassium acetate (4.6 g) in glacial acetic acid (7.5 ml). After evaporation of acetic acid the residue was treated with water (15 ml) and ether (40 ml), the ethereal layer washed with 10% K_2CO_3 solution, water, dried, concentrated, and the residue distilled at 111-113° (4 mm). Yield 8.7 g (83%).

Found %: C 48.85; H 7.35; S 14.07. $C_9H_{16}O_4S$. Calculated %: C 49.09; H 7.35; S 14.54.

Ethyl ester of γ-hydroxypropylmercaptoacetic acid (III). 3.5 g of substance (II) was saponified by boiling with 10% alcohol KOH solution (30 ml) for 3 hours. The resulting hydroxy acid was not isolated but was immediately esterified by heating with anhydrous alcohol (40 ml) containing conc. H_2SO_4 (3 g). After evaporation of alcohol in vacuo the residue was treated with water (15 ml) and ether (25 ml). The ethereal layer was washed with 10% K_2CO_3 solution, water, dried and concentrated. The residue distilled at 127-130° (3.5 mm). Yield 3.1 g (46%), calculated on initial (II).

Found %: C 47.22; H 8.26; S 17.37. $C_7H_{14}O_3S$. Calculated %: C 47.19; H 7.86; S 17.97.

γ-Aminopropylmercaptoacetic acid (VI). Thioglycolic acid (19.5 g), the hydrobromide of 1-amino-3-bromopropane* (45 g), and 2 N NaOH (310 ml) were stirred at room temperature for 12 hours. The solution was neutralized with 2 N HBr (pH 6.5-7.0), concentrated in vacuo, the crystalline residue treated a number of times with boiling anhydrous methyl alcohol (about 1 liter). The insoluble amino acid (VI) (22.7 g) was recrystallized from 70% alcohol. Yield 16.8 g (55%), m.p. 198° (with slow heating).

Found %: C 40.41; H 7.60; S 20.71; N 9.57. $C_5H_{11}O_2NS$. Calculated %: C 40.2; H 7.2; S 21.4; N 9.39.

Hydrochloride of γ-aminopropylmercaptoacetic acid (VII). 1 g of substance (VI) was dissolved in conc. HCl (3 ml), and wetted with acetone; a colorless substance immediately crystallized out, m.p. 137-138.5°. Yield 1.15 g.

Found %: N 7.78, 7.69. $C_5H_{12}O_2NSCl$. Calculated %: N 7.52.

N-benzoyl-γ-aminopropylmercaptoacetic acid (VIII). To a solution of (VI) (2.22 g) in water (40 ml) was added $NaHCO_3$ (12.3 g); to the resulting suspension benzoyl chloride (6.25 g) was added dropwise with stirring; stirring was continued for 4 hours, the solution acidified with concentrated hydrochloric acid to pH 2.0; the resulting

* Obtained similarly to 2-bromoethylamine [10].

precipitate was filtered by suction, washed with water, and dried. After a number of treatments with boiling petroleum ether an oily precipitate remained, which was extracted with ether on a rocker. After concentrating the extract (50 ml) the residue crystallized, m.p. 78-82°.

Found %: N 5.59, 5.41. $C_{12}H_{15}O_3NS$. Calculated %: N 5.52.

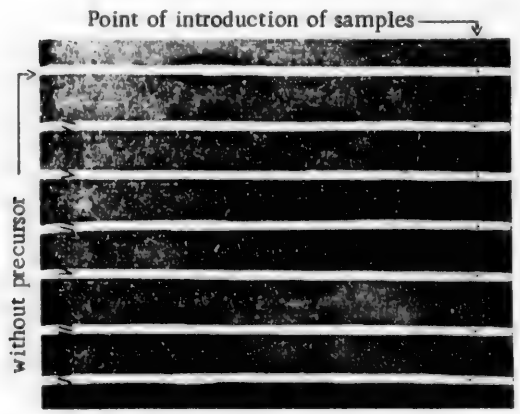
Sulfone of γ-aminopropylmercaptoacetic acid (IX). To a solution of substance (VI) (0.5 g) in glacial acetic acid (5 ml) was added 30% hydrogen peroxide (2 ml); after standing in the dark for 20 days the solution was concentrated in vacuo at room temperature. The resulting crystalline substance was washed with glacial acetic acid, and recrystallized from 40% aqueous alcohol, m.p. 161-163°.

Found %: N 7.73, 7.85. $C_5H_{11}O_4NS$. Calculated %: N 7.73.

Lactam (X). a) To a solution of ethyl sodiummercaptoacetate (from 6 g of ester and 1.15 g of Na) in anhydrous alcohol was added, with stirring, an alcoholic solution of 1-amino-3-bromopropane (obtained from 11 g of hydrobromide), and the reaction solution then boiled for 4 hours, this being accompanied by formation of sodium bromide. Alcohol was evaporated off in vacuo, the residue treated three times with chloroform (in 50 ml lots), the latter evaporated off. The crystalline residue of (X) was washed with alcohol and ether, m.p. 141-142.5°. Yield 3.9 g (60%).

Found %: C 46.18; H 7.24; S 24.00; N 10.36. C_5H_9ONS. Calculated %: C 45.80; H 6.87; S 24.42; N 10.68.

b) 3 g of substance (VI) was wetted with anhydrous alcohol (30 ml) containing HCl (15%). After standing the solution overnight alcohol was evaporated off in vacuo at room temperature. The remaining oil was wetted with ether (30 ml), the ethereal solution cooled with ice, washed with 25% ammonia solution, and dried. The oil remaining after evaporation of ether crystallized on standing, m.p. 141-142.5°. A sample mixed with substance (X) showed no melting point depression.



Chromatograms of culture liquid, obtained in the system butanol–ethanol–water.

Hydrolysis of lactam (X). 1 g of the substance was heated with conc. HCl (5 ml) for 4 hours, the solution then concentrated in vacuo, the oily residue rapidly crystallized, and washed with acetone, m.p. 137-138°. A sample mixed with hydrochloride (VII) showed no melting point depression.

Ethyl ester of γ-nitropropylmercaptoacetic acid (XII). To the ethyl ester of thioglycolic acid [4] (3 g) were added, with stirring, dry sodium alcoholate (0.01 g) and nitroallyl [11] (4.35 g), whereupon the temperature rose spontaneously from 20 to 28°. After standing at room temperature for 16 hours, unreacted initial substances were evaporated from the reaction mixture in vacuo (5-7 mm, 70°). The residue was treated with 4-5 ml of water, and extracted with ether. After concentrating the ethereal extract the remaining oil was dissolved in anhydrous alcohol (4-5 ml); after adding an alcoholic solution of sodium alcoholate a yellow precipitate of the sodium salt of (XII) (0.7 g) gradually formed on standing.

Found %: N 6.00, 6.05. $C_7H_{12}O_4NSNa$. Calculated %: N 6.11.

Formation of new penicillins. Fermentation was carried out in a synthetic medium of Penicillium chrysogenum, strain "New Hybrid" [12]. Substances tried as precursors were introduced into the medium at a concentration of 0.05-0.1%. Total amount of penicillins formed was determined iodometrically, composition of the penicillins formed – by paper chromatography [13]. Two solvent systems were used in the chromatography: ether–water (5 : 1) and butanol–ethanol–water (4 : 1 : 5). Chromatograms were developed bioautographically. Formation of new penicillins on addition of the substance under trial was inferred from the increase in amount of penicillin compared with a control without precursor and by appearance of a new spot on the chromatogram. As an example, chromatograms are shown of penicillins formed in the culture liquid in presence of precursors (illustration).

SUMMARY

1. A series of new derivatives of propyl- and ethylmercaptoacetic acids was synthesized, containing various functional groups in the propyl and ethyl radicals.

2. It was established that on esterification of γ-aminopropylmercaptoacetic acid (VI), instead of the ethyl ester $C_7H_{15}O_2NS$, a crystalline substance C_5H_9ONS (X) is formed, giving a hydrochloride (VII) on hydrolysis. It is possible that (X) is a sulfur-containing, cyclic, seven-membered lactam.

3. Compounds (I-VI), (VIII), (IX), (XIII-XVI) were studied as possible precursors in penicillin biosynthesis. From fermentation experiments with the fungus Penicillium chrysogenum it was established that all the substances enumerated, except (I) and (XV), were used by the microorganism with formation of a series of new penicillins, characterized by differing antibacterial activity.

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INVESTIGATION IN THE FIELD OF ANTIBIOTIC PRECURSOR AND FRAGMENT SYNTHESIS

V. SYNTHESIS OF DI- AND TRIHALOGEN DERIVATIVES OF CYCLOHEXENECARBOXYLIC ACID

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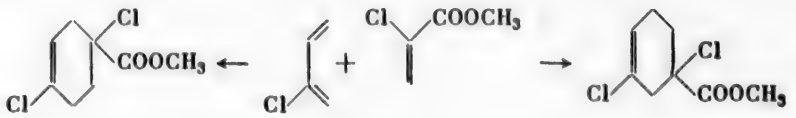
In a previous communication [1] an ester of 1,3,4,5-tetrachlorocyclohexenecarboxylic acid was described, obtained by us as an intermediate product in synthesis of quinic acid. To achieve certain stages in the synthesis of this acid we had to synthesize as models a series of halogen-containing acids of the cyclohexene series not described in the literature. In the present communication the synthesis is described of methyl esters of di- and trihalogen derivatives of cyclohexenecarboxylic acids obtained by diene condensation. As dienes, chloroprene and 1,2,3-trichlorobutadiene were used, and the dienophils – the methyl esters of acrylic, methylacrylic, and α-chloroacrylic acids.

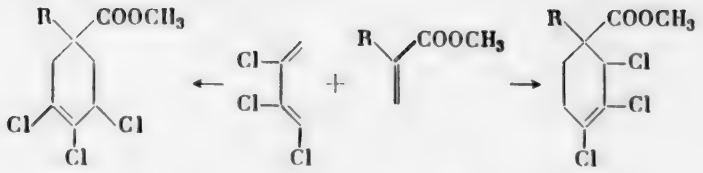
On condensing chloroprene with the methyl ester of α-chloroacrylic acid a product of composition $C_8H_{10}O_2Cl_2$ (I) was obtained. As a result of the reaction, formation could be expected of two structural isomers of an adduct of para- and meta-structure.



Proof of the structure of the substance obtained was based on bromination of the previously saponified ester of N-bromosuccinimide with subsequent dehydrohalogenation with triethylamine. As a result, p-chlorobenzoic acid was obtained, which gave no melting point depression with an authentic sample. Thus, we succeeded in showing that the reaction proceeds in the direction of formation of a compound of para-structure.

In addition, it should be noted that on saponification of the adduct we obtained an acid which appeared identical with 4-chloro-$\Delta^{1,4}$-dihydrobenzoic acid described in the literature [2]. Consequently, under these conditions saponification is accompanied by dehydrochlorination of the labile chlorine attached to the carbon with a carboxyl group. Preparation of this acid was a further indication of formation of a product of para-structure. The adduct is readily converted into the amide of 1,4-dichloro-Δ^3-cyclohexenecarboxylic acid. Preparation of the amide takes place under milk conditions and is not accompanied by dehydrochlorination. The results obtained agree with data in the literature on similar diene syntheses. Thus, on condensing chloroprene with acrylic acid [3, 4] and its derivatives [5] in most cases the meta-isomers are not found among the reaction products, or the isomers are present in insignificant amounts.

As shown by us previously [1], diene condensation of trichlorobutadiene with the methyl ester of α-chloroacrylic acid proceeds with formation of an adduct of symmetrical structure. Continuing our investigations in this direction, we studied condensations of trichlorobutadiene with the methyl esters of acrylic and methacrylic acids. In this case substances were obtained of composition $C_8H_9O_2Cl_3$ (II) and $C_9H_{11}O_2Cl_3$ (III) respectively. In both reactions, of the two possible structural isomers of adducts (A, B) only one isomer was obtained.



(A) R = H, (B) R = CH_3

To prove the structure of compound (II), as in the case of substance (I) also, bromination of the adduct with N-bromosuccinimide and dehydrohalogenation with triethylamine were carried out. After saponification, 3,4-dichlorobenzoic acid was obtained, i.e., in this case the reaction proceeds with formation of an adduct of symmetric structure. From the results obtained and the data in the literature [1] it can be proposed that condensation of trichlorobutadiene and the methyl ester of methylacrylic acid proceeds with formation of an adduct of similar structure.

EXPERIMENTAL •

Initial substances: 1,2,3-trichlorobutadiene-1,3 [b.p. 56-60° (26 mm), n_D^{20} 1.5262] was prepared by the method mentioned in [6]; methyl ester of α-chloroacrylic acid [b.p. 41-44° (28 mm), n_D^{20} 1.4420]; methyl ester of acrylic acid (b.p. 80°, n_D^{20} 1.3984); methyl ester of methylacrylic acid (b.p. 100°, n_D^{20} 1.413); chloroprene (b.p. 59°, n_D^{20} 1.4583). Condensation was carried out in sealed ampoules.

Condensation of chloroprene with methyl ester of α-chloroacrylic acid. In an ampoule were placed 0.1 g of hydroquinone, 17.7 g (0.2 mole) of freshly distilled chloroprene, and 24.0 g (0.2 mole) of freshly distilled methyl α-chloroacrylate and heated in a thermostat at 80° for 48 hours. A dark-yellow oil formed, from which in vacuo was evaporated off unreacted diene and dienophil (boiling azeotropically). On further distillation of the condensation product a fraction was obtained with b.p. 77-90° (5 mm) in amount 14.3 g. The latter was fractionally distilled (20 theoretical plates), the main fraction having b.p. 89-90° (2 mm). A colorless, clear oil, readily soluble in organic solvents, sparingly soluble in water.

n_D^{20} 1.5022, d_4^{20} 1.2855, MR_D 47.9; calc. 47.29. U.v.-spectrum: λ_{max} 225 mμ; $E_{1cm}^{1\%}$ 403.2 (butanol).

Found %: C 46.28, 46.23; H 4.92, 4.92; Cl 34.41, 34.39. $C_8H_{10}O_2Cl_2$. Calculated %: C 45.93; H 4.78; Cl 33.97.

Saponification of methyl ester of 1,4-dichloro-Δ^3-cyclohexenecarboxylic acid. 10.4 g of the substance was boiled for 1.5 hours with 50 ml of 40% caustic soda solution, 50 ml of concentrated hydrochloric acid added and extracted with ether. The ethereal solution was dried with $MgSO_4$, ether distilled off, and 8.7 g (89.4%) of a crystalline substance obtained. After recrystallizing twice from acetone and alcohol, m.p. was 217-218°. According to the data in the literature [2] 4-chloro-$\Delta^{1,4}$-dihydrobenzoic acid has m.p. 216-217°.

Found %: C 53.27, 53.40; H 4.65, 4.66; Cl 21.95, 21.83. $C_7H_7O_2Cl$. Calculated %: C 53.0; H 4.43; Cl 22.40.

U.v.-spectrum: λ_{max} 236-237 and 298-299 mμ, respectively, $E_{1cm}^{1\%}$ 97.8 and 252.4 (butanol).

Preparation of amide of 1,4-dichloro-Δ^3-cyclohexenecarboxylic acid. 5.0 g of substance (I) and 15 ml of 15% alcoholic ammonia solution were heated in a sealed ampoule for 5 hours at 40°. Alcohol was then evaporated off and 4.0 g (86%) of a crystalline substance obtained, which after recrystallizing three times from methanol had m.p. 108-109°.

Found %: N 7.22, 7.58. $C_7H_9ONCl_2$. Calculated %: N 7.21.

Preparation of p-chlorobenzoic acid. 1.8 g (0.0112 mole) of 4-chloro-$\Delta^{1,4}$-dihyrobenzoic acid was heated (by the method described in [3]) with 2.0 g (0.0112 mole) of N-bromosuccinimide and 0.1 g of benzoyl peroxide in 30 ml of benzene for 6 hours. Then, without isolating the product, it was dehydrohalogenated with 17.2 g (0.17 mole) of triethylamine (heating for 4 hours). After acidification, 1.5 g of a crystalline substance was obtained with

• With participation by V. V. Konstantinova.

m.p. 235° (after recrystallizing twice from alcohol). A sample mixed with an authentic sample of p-chlorobenzoic acid gave no melting point depression.

Found %: C 53.28; 53.35; H 3.00, 3.02; Cl 22.95, 23.04. $C_7H_5O_2Cl$. Calculated %: C 53.6; H 3.19; Cl 22.6.

Condensation of 1,2,3-trichlorobutadiene-1,3 with methyl ester of acrylic acid. In an ampoule were placed 0.1 g of hydroquinone, 15.7 g (0.1 mole) of freshly distilled trichlorobutadiene, and 7.6 g (0.1 mole) of freshly distilled methyl acrylate. The ampoule, filled with nitrogen and sealed, was placed in a thermostat, where it was heated at 120° for 48 hours. A dark-yellow oil formed, from which was distilled off in vacuo unreacted diene and dienophil, which boiled azeotropically. On further distillation of the condensation product a fraction was obtained with b.p. 128-135° (5 mm)–9.9 g. To free it from hydroquinone, the adduct was treated with soda solution, as in the work [1]. A second distillation with a large fractionating column gave a colorless oil, boiling mainly at 131-132° (5 mm). On prolonged standing in the cold the oil crystallized completely. The crystals were carefully washed on a filter with petroleum ether, dried in a vacuum-desiccator over paraffin. M.p. 40.5°, readily soluble in organic solvents and with difficulty in water.

U.v.-spectrum: λ_{max} 221 mμ; $E^{1\%}_{1cm}$ (butanol).

Found %: C 39.66, 39.84; H 3.72, 3.83; Cl 43.81, 43.62. $C_8H_9O_2Cl_3$. Calculated %: C 39.42; H 3.69; Cl 43.73.

Expt. No.	Diene			Dienophil			Yield of adduct (in g)	Ratio of diene and dienophil
	name	amount (in g)	amount (in moles)	name	amount (in g)	amount (in moles)		
1	Chloroprene	17.7	0.2	Methyl ester of α-chloroacrylic acid	24.0	0.2	14.3	1:1
2	" "	4.0	0.045	Ditto	33.0	0.27	7.3	1:6
3	" "	29.0	0.32	" "	5.0	0.040	8.8	8:1
4	Trichlorobutadiene	15.7	0.1	Methyl ester of acrylic acid	7.6	0.1	9.9	1:1
5	Ditto	4.0	0.0253	Ditto	20.0	0.263	4.6	1:10
6	" "	49.0	0.31	" "	4.0	0.040	7.9	7.7:1
7	" "	14.0	0.088	Methyl ester of methacrylic acid	8.8	0.088	6.6	1:1
8	" "	4.5	0.0285	Ditto	28.6	0.0286	4.0	1:10
9	" "	38.7	0.246	" "	4.5	0.045	6.1	5.4:1

Preparation of 3,4-dichlorobenzoic acid. 3.0 g (0.012 mole) of substance (II) was heated by the method described in [3] at 80° for 6 hours with 4.3 g (0.024 mole) of N-bromosuccinimide and 0.1 g of benzoyl peroxide in 30 ml of benzene. Without isolating the product, it was dehydrohalogenated with 35 g of triethylamine (0.34 mole), heating for 4 hours. The resulting oil was saponified with 30 ml of 10% aqueous caustic soda solution (heating for 2 hours at 80°). After acidification and extraction with ether 0.8 g of crystals was obtained, m.p. 201° (from chloroform). A sample mixed with 3,4-dichlorobenzoic acid gave no melting point depression.

Found %: C 44.21, 44.18; H 2.30, 2.28; Cl 36.68, 36.79. $C_7H_4O_2Cl_2$. Calculated %: C 43.97; H 2.09; Cl 37.17.

Condensation of trichlorobutadiene with methyl ester of methylacrylic acid. The reaction was carried out under conditions similar to the foregoing. From 14.0 g (0.088 mole) of freshly distilled trichlorobutadiene and 8.8 g (0.088 mole) of freshly distilled methyl methylacrylate was obtained a fraction with b.p. 140-152° (5 mm)–6.6 g.

After a second distillation with a large fractionating column an oil was obtained, boiling mainly at 149-150° (5 mm). On prolonged standing in the cold the oil crystallized completely. The crystals were carefully washed on a filter with anhydrous alcohol and petroleum ether, and dried in a vacuum-desiccator over paraffin. M.p. 59°, readily soluble in organic solvents, with difficulty in water.

U.v.-spectrum: λ_{max} 222 mμ; $E^{1\%}_{1\,cm}$ 240.5 (butanol).

Found %: C 41.94, 42.08; H 4.41, 4.40; Cl 40.83, 40.86. $C_9H_{11}O_2Cl_3$. Calculated %: C 41.94; H 4.27; Cl 41.35.

On distilling all the adducts, unreacted diene and dienophil boiled azeotropically, thus it was difficult to estimate the reacted reagents. To determine yields more precisely, additional experiments were needed with a 6-10 fold excess of one of the reagents. Results of a series of experiments are given in the table. According to experiment 2, yield of substance (I) amounted to 77% on the diene. From experiment 5 it follows that yield of substance (II) was equal to 73.4% on the diene. Experiment 8 shows that substance (III) was obtained in 54.4% yield on the diene.

SUMMAY

1. A study was made of the diene condensation of the chloroprene with the methyl ester of α-chloroacrylic acid and of trichlorobutadiene with the methyl esters of acrylic and methacrylic acids.

2. The structure was established of the condensation products obtained, these being respectively the methyl esters of 1,4-dichloro-3,4,5-trichloro-, and 1-methyl-3,4,5-trichloro-Δ^3-cyclohexenecarboxylic acids. These compounds have not been described in the literature.

3. It was proved that the reaction proceeds with formation of para-isomers and adducts of symmetrical structure.

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INVESTIGATION IN THE FIELD OF ANTIBIOTIC PRECURSOR AND FRAGMENT SYNTHESIS

VI. DERIVATIVES OF MERCAPTOACETIC ACID CONTAINING LACTAMS

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and F. P. Sidel'kovskaya

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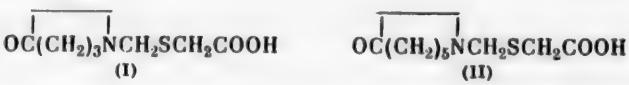
pp. 1463-1465, May, 1961
Original article submitted June 20, 1960

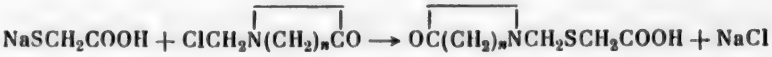
It is known that mercaptoacetic acids of general formula $RSCH_2COOH$ and their esters $RSCH_2COOR'$ are in the majority of gases precursors in penicillin synthesis and are used by microorganisms on introducing them into the culture medium. A large number of mercapto compounds with the above general formula have been described, R having a very varied structure (of the aliphatic, aromatic, and heterocyclic series with or without substituents in the chain) [1, 2]. It was of interest to synthesize substituted mercaptoacetic acids and their esters in which R contains a lactam ring, and to elucidate the effect of this ring on the properties of the mercaptoacetic acid as a penicillin precursor. Similar compounds have not been described in the literature.

In the present work were synthesized N-pyrrolidonylmercaptoacetic acid (I), 2-oxopentamethylene-1-iminomethylmercaptoacetic acid (II) and their esters.



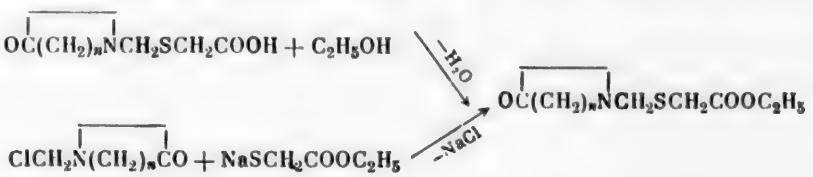
(I) (II)

The acids were prepared by the action of a mercaptide of thioglycolic acid on the N-chloromethyl lactams described previously [3].



In this reaction use is made of the high lability of the halogen atom in N-chloromethyl lactams, established in the case of hydrolysis and alcoholysis [3]. In view of the ready saponifiability of the chlorides indicated, the process was carried out in a dry benzene or dioxane medium. In this connection, the mercaptide of thioglycolic acid was prepared by reacting the latter with metallic sodium in benzene as distinct from the widely used method for similar reactions in mercaptide preparation, consisting of treatment of thioglycolic acid with aqueous caustic soda solution [4]. Formation of lactam-containing acids proceeds exceedingly readily and is accompanied by evolution of heat. The acids indicated are formed in yields up to 70%.

To prove that compounds (I) and (II) have a free carboxyl group, their esters were prepared by direct esterification with alcohol. In addition, the esters indicated were prepared by counter synthesis by reacting the mercaptide of the ethyl ester of mercaptoacetic acid with N-chloroalkyl lactams.



To obtain the N-substituted carboxylic acid of formula $HO_2C(CH_2)_5NHCH_2SCH_2COOH$ (III), hydrolysis was carried out of 2-oxopentamethylene-1-iminomethylmercaptoacetic acid with hydrochloric acid of various concentrations (12, 3, and 1.7%). However, instead of the proposed acid (III) the hydrochloride of ε-aminocaproic acid was obtained even on heating with dilute hydrochloric acid (concentration 1.7%). Evidently the presence of a sulfur and a nitrogen atom on the same carbon atom renders this compound rather unstable, as a result of which considerable decomposition takes place under the action of the dilute acid.

EXPERIMENTAL

2-Oxopentamethylene-1-iminomethylmercaptoacetic acid (II). To a suspension of 7 g (0.061 mole) of the Na-derivative of mercaptoacetic acid in 50 ml of anhydrous benzene was added with stirring 9.87 g (0.061 mole) of N-chloromethyl lactam, whereupon the temperature spontaneously rose from 20 to 38°. The reaction mixture was stirred for 5 hours at 79-82°, then cooled and filtered from sodium chloride. The resulting benzene solution was treated with 10% aqueous caustic soda (to pH 9.0). The aqueous-alkaline layer was separated, washed with ether to remove traces of benzene, acidified with 10% hydrochloric acid (to pH 2.0). An oily layer then separated, which crystallized rapidly and was 2-oxopentamethylene-imino-methylmercaptoacetic acid. The substance was filtered off, recrystallized from ether (35 ml of ether per 0.3 g of the substance). M.p. 87.5-88.5°. Yield 7.4 g. An additional 2.1 g of (II) was obtained from the acidic aqueous mother liquor. Total yield 9.5 g (70%). Sparingly soluble in ether, petroleum ether, soluble in chloroform, benzene, water, alcohol, acetone.

Found %: C 50.30; H 6.98; N 6.39; S 14.78. $C_9H_{15}O_3NS$. Calculated %: C 50.23; H 6.98; N 6.40; S 14.88.

By concentrating the benzene layer by evaporation in vacuo at 80-100 mm, 1.45 g of N-methylolcaprolactam was obtained, m.p. 64-65.5° (data in the literature 64-65.5° [3]).

N-Pyrrolidonylmercaptoacetic acid (I). To a suspension of 8.85 g (0.077 mole) of the Na-derivative of mercaptoacetic acid in 50 ml of anhydrous benzene was added with stirring for 20 minutes 10.3 g (0.077 mole) of N-chloromethylpyrrolidone; the temperature then rose spontaneously from 20 to 41°. The reaction mixture was then treated in a manner similar to that of the foregoing experiment. 7.5 g (50%) of (I) was obtained with m.p. 110-111° (from anhydrous acetone: 8 ml of anhydrous acetone per 0.25 g of the substance).

Found %: C 44.76; H 6.01; N 7.24; S 16.62. $C_7H_{11}O_3NS$. Calculated %: C 44.44; H 5.82; N 7.40; S 16.93.

Soluble in water, alcohol, acetone, chloroform, dioxane, soluble with difficulty in heptane, petroleum ether, sulfuric ether.

Ethyl ester of 2-oxopentamethylene-1-iminomethylmercaptoacetic acid. a) Esterification of 2-oxopentamethylene-1-iminomethylmercaptoacetic acid. 1.7 g of (II) was boiled with 5 ml of anhydrous alcohol for 4.5 hours in presence of 0.1 ml of sulfuric acid, then most of the alcohol distilled off in vacuo at 80-100 mm. The residue was poured into aqueous soda solution, the ester extracted twice with sulfuric ether, the ethereal extract dried over anhydrous sodium sulfate. The sulfuric ether was evaporated off, the residue twice distilled at 170-171° (3 mm). 0.9 g (43%) of ester was obtained, n_D^{19} 1.5102. Insoluble in water, soluble in sulfuric ether, petroleum ether, benzene, chloroform, alcohol.

Found %: C 54.11; H 7.93; N 5.80; S 12.59. $C_{11}H_9O_3NS$. Calculated %: C 53.80; H 7.75; N 5.71; S 13.06.

b) Reaction of sodiummercaptoaceticethyl ester of with N-chloromethyl lactam. To a suspension of 2.4 g of sodiummercaptoaceticethyl ester in 25 ml of anhydrous benzene was added 2.7 g of N-chloromethylcaprolactam, the reaction mixture stirred for 4 hours at 79-82°, cooled, filtered. After evaporation of benzene, the residue distilled at 170-171° (3 mm). Yield of ester 1.5 g (49%), n_D^{19} 1.5109.

Ethyl ester of N-pyrrolidonylmercaptoacetic acid. a) Esterification of N-pyrrolidonylmercaptoacetic acid. Similarly to the above-described, from 1.3 g of (I) and 5 ml of anhydrous alcohol 0.7 g (50%) was obtained, b.p. 159-160° (3 mm), n_D^{19} 1.5058.

Found %: C 49.81; H 7.12; N 6.62; S 14.35. $C_9H_{15}O_3NS$. Calculated %: C 49.76; H 6.91; N 6.45; S 14.74.

Insoluble in water, petroleum ether, soluble in sulfuric ether, alcohol, chloroform, benzene, acetone.

b) Reaction of sodiummercaptoaceticethyl ester with N-chloromethylpyrrolidone. To a suspension of 2.4 g of sodiummercaptoaceticethyl ester in 25 ml of anhydrous benzene was added 2.25 g of N-chloromethylpyrrolidone, the reaction mixture stirred for 4 hours at 79-82°, cooled, filtered. After evaporation of benzene the residue distilled at 159-160° (3 mm). Yield 1.8 g (50%), n_D^{19} 1.5058.

Hydrolysis of 2-oxopentamethylene-1-iminomethylmercaptoacetic acid. 0.95 g of (II) with 16.3 ml of 1.7% hydrochloric acid was boiled with reflux condenser for 1 hour; the solution was concentrated by evaporation, and the crystalline residue, the hydrochloride of ε-aminocaproic acid, recrystallized from a mixture of anhydrous alcohol and ether (1 : 1). M.p. 128-129°. Yield 0.7 g (90%).

Found %: C 43.45; H 8.81; N 8.40. $C_6H_{14}O_2NCl$. Calculated %: C 42.98; H 8.36; N 8.36.

SUMMARY

1. N-Pyrrolidonyl- and 2-oxopentamethylene-1-iminomethylmercaptoacetic acids and their esters were synthesized.

2. Hydrolysis of 2-oxopentamethylene-1-iminomethylmercaptoacetic acid was studied; under the influence of dilute hydrochloric acid it decomposes to the hydrochloride of ε-aminocaproic acid.

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IMIDAZOLE DICARBOXYLIC ACID DERIVATIVES

I. ALKYLATION OF AMIDE OF IMIDAZOLE-4,5-DICARBOXYLIC ACID

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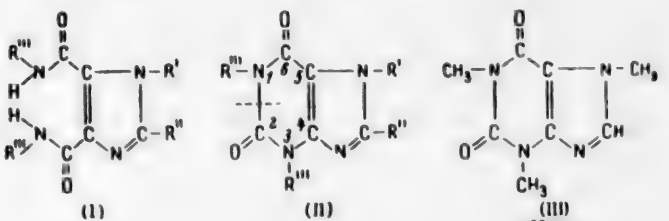
In the search for new substances possessing selective action on the central nervous system, systematic synthesis of alkylated amides of imidazole-4,5-dicarboxylic acids (I) was undertaken [1]. These compounds can be regarded as "open" structural analogs of xanthine derivatives (II), in which the atoms, carbon 2 and nitrogen 3, of the pyrimidine ring together with their substituents are rearranged, but the imidazole ring retained completely.



(I) (II) (III) Caffeine

The considerations mentioned later, confirming the importance of the influence of the imidazole ring on the character of the physiological action of xanthine derivatives, are the reasons for synthesis of compounds of type (I). Bicyclic structural analogs of caffeine (III), related both to the imidazolopyrimidine class (IV) and to the pyrazolopyrimidine class (V), in this and in other ways possess a caffeine-like action, none of these compounds achieving the effectiveness of caffeine in action on the central nervous system.

(IV) (V)

a) 1,3,9-CH_3, 2,6-O } Isocaffeine [1]

b) 1,3,7-CH_3, 6,8-O } c) 1,7,9-CH_3, 2,8-O } Trimethyldioxotetrahydropurines [1, 2]

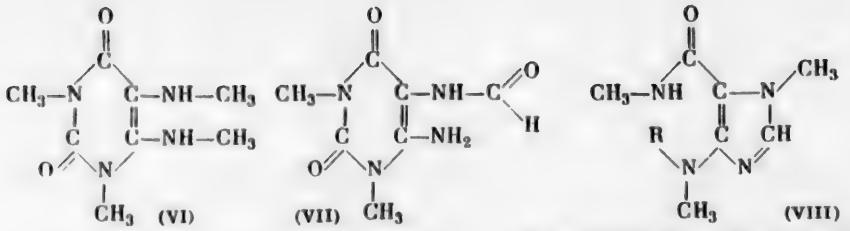
d) 1,3,7,8-CH_3, 2,6-O } 8-Methylcaffeine [3]

e) 1,3,7-CH_3, 2,6,8-O } Oxycaffeine [4, 5]

a) 2,5,7-CH_3, 4,6-O

b) 1,5,7-CH_3, 4,6-O } Pyrazolopyrimidines [6]

In addition to bicyclic structural analogs of caffeine, two types of its monocyclic or "open" analogs are known also: pyrimidine (VI) and imidazole (VIII) types.

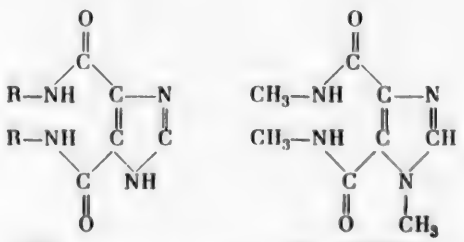


(VI) (VII) (VIII)

a) R = COOH, b) R = H, c) R = CH_3.

Of compounds close to the first group, only a theophylline analog has been investigated pharmacologically – 1,3-dimethyl-4-amino-5-formaminouracil (VII), which appeared physiologically inactive [7]. At the same time, the imidazole structural analogs of caffeine – caffeidine (VIIIa) and caffeidinecarboxylic acid (VIIIb) retain some of the elements of the pharmacological action of caffeine, although it is considerably weakened [5,8]. In connection with the above-mentioned, it can conjectured that as a result of synthesis of compounds such as type (I) could be obtained possessing an action on the central nervous system similar or opposite to caffeine.

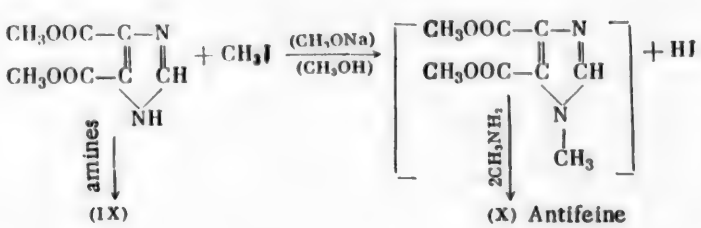
In the present communication the synthesis is described of three dialkyldiamides of imidazole-4,5-dicarboxylic acid (IX a, b, c) and of the dimethyldiamide of 1-methylimidazole-4,5-dicarboxylic acid (X). The latter compound (it has been given the same "antifeine") can be regarded as the open imidazole analog of caffeine with rearrangement of C and N atoms.



(IX) (X) Antifeine

a) R = CH_3, b) R = C_2H_5, c) R = C_4H_9.

The initial substance in synthesis of these compounds was imidazole-4,5-dicarboxylic acid, obtained by oxidation of benzimidazole with potassium bichromate in a sulfuric acid medium [9]. Conversion from imidazole-4,5-dicarboxylic acid to its substituted amides (IX) was achieved via the ester since, according to the data in the literature [10], preparation of the di-acid chloride of imidazole-4,5-dicarboxylic acid is not possible. The dimethyl ester of imidazole-4,5-dicarboxylic acid was prepared by esterification in a stream of hydrogen chloride [10]. Dialkylamides (IX) were formed by the action of amines on this ester.



(IX) (X) Antifeine

Pharmacological study of the compounds obtained* showed that dialkyldiamides of imidazole-4,5-dicarboxylic acid (IX) possess a stimulating action on the brain cortex [11, 12]. However, the action of these compounds is weaker than the action of caffeine.

* The study of the pharmacological properties of all the compounds obtained was carried out by Yu. S. Borodkin.

To prepare antifeine (X), which possesses a considerably greater structural similarity to caffeine than the dialkyldiamides (IX), the ester of imidazole-4,5-dicarboxylic acid was methylated with methyl iodide in presence of sodium methylate [10]. The resulting ester of 1-methylimidazole-4,5-dicarboxylic acid was not isolated from solution, but immediately converted into the dimethyldiamide by the action of aqueous methylamine solution. In the course of the synthesis it was established that methylation of the ester of imidazole-4,5-dicarboxylic acid can be achieved with both methyl iodide and bromide. (In the latter case about a 10 fold excess of alkyl halide was used because it was passed through the reaction mixture during the entire period of alkylation) Yield of purified antifeine obtained by both methods was approximately identical and amounted to 52-56%, calculated on the initial ester of imidazole-4,5-dicarboxylic acid.

The structure of antifeine was proved by quantitative (99.6%) collection of methylamine evolved on alkaline saponification of this compound in a Kjeldahl apparatus [13]. This method can be used for quantitative determination of antifeine applied under production conditions. From the acidified solution after saponification of antifeine 1-methylimidazole-4,5-dicarboxylic acid can be isolated. In this case, it is desirable to use a smaller excess of alkali for hydrolysis than in quantitative determination.

Pharmacological investigation of antifeine showed that this compound in its action on the brain cortex exhibits the properties of an antagonist of caffeine [11] and in this respect is of utmost interest in practical use in medicine. It is at present being subjected to clinical trials as a sedative, i.e., as a tranquilizing agent.

EXPERIMENTAL

Imidazole-4,5-dicarboxylic acid was prepared by the method described in [9], starting with 40 g of benzimidazole. Yield averaged 31.55 g (59%), calculated on initial benzimidazole. The acid was reprecipitated from a hot ammoniacal solution of its ammonium salt by hydrochloric acid. Yield of purified acid 25.58 g (48.6%).

Dimethyl ester of imidazole-4,5-dicarboxylic acid [10]. In a three-necked 0.5 liter flask were placed 40 g of dry purified imidazole-4,5-dicarboxylic acid and 400 ml of dry methanol. The mixture was heated on a water bath with reflux condenser and stirrer until the methanol boiled gently. Through the system was bubbled a stream of dry hydrogen chloride until the deposit of acid dissolved. The reaction mixture was neutralized with saturated soda solution to pH 6-7 at 2-10°, mechanically stirred, and acidified with acetic acid to pH 4. The precipitate settling out of the ester of imidazole-4,5-dicarboxylic acid was filtered off and recrystallized from 1 liter of distilled water with addition of 5 ml of acetic acid. Yield of purified ester 24.4 g (51.8%, calculated on initial imidazole-4,5-dicarboxylic acid).

Dimethyldiamide of imidazole-4,5-dicarboxylic acid (IXa).* 4.9 g of the ester of imidazole-4,5-dicarboxylic acid was shaken with 40 ml of 20% aqueous methylamine solution until the ester deposit dissolved. The solution was left overnight to complete the reaction. On the following day the solution was neutralized with cooling with concentrated hydrochloric acid, added dropwise to pH 4. The white precipitate of dimethyldiamide settling out was filtered off and air dried. Yield of dry unpurified product 4.4 g (90%). The substance was recrystallized three times from water, the first time using activated carbon. Yield of purified compound 71%. M.p. 220-221°.

Found %: N 30.73; C 46.17; H 5.31. $C_7H_{10}O_2N_4$. Calculated %: N 30.76; C 46.14; H 5.53.

Diethyldiamide of imidazole-4,5-dicarboxylic acid (IXb). The compound was obtained similarly to the foregoing, starting from 7 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid. An aqueous ethylamine solution with a concentration of 0.2 g/ml was used (25 ml). To purify the diethyldiamide four recrystallizations from water were necessary, the first time using carbon. The purified compound took the form of fine, white crystals (on rapid crystallization) or long, white, fibrous crystals (on slow crystallization). Melting point of both crystalline forms 144-145°. A mixed sample of them showed no melting point depression. Yield of purified compound 30.4%.

Found %: N 26.42; C 51.39; H 6.81. $C_9H_{14}O_2N_4$. Calculated %: N 26.65; C 51.41; H 6.71.

Dibutyldiamide of imidazole-4,5-dicarboxylic acid (IXc). 4 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid was heated with 15 ml of methanol to partially dissolve it, then to the reaction mixture was added 6 ml of butylamine, and the mixture heated with reflux condenser on a water bath for 15 minutes. On the following day,

* The dimethyldiamide of imidazole-4,5-dicarboxylic acid and "antifeine" (X) were initially prepared by L. R. Davidenkov [14].

excess methanol and butylamine were removed on a water bath, and the residue recrystallized from water. 1.5 g was obtained of unreacted ester of imidazole-4,5-dicarboxylic acid, identified by melting point and a mixed sample. The mother liquor after concentration by evaporation took the form of an oil, solidifying on cooling. This substance was recrystallized four times from aqueous alcohol. 1.5 g of white crystals was obtained with m.p. 133-134°. Yield 40.5% (on reacted ester of imidazole-4,5-dicarboxylic acid).

Found %: N 20.90. $C_{13}H_{22}O_2N_4$. Calculated %: N 21.05.

Dimethyldiamide of 1-methylimidazole-4,5-dicarboxylic acid or antifeine (X). Method A [10, 14]. 10 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid was dissolved by stirring and boiling with reflux condenser in 4500 ml of dry methanol. A methanol solution of sodium methylate was prepared separately by dissolving 13 g of sodium in 150 ml of methanol. The solution of the ester of imidazole-4,5-dicarboxylic acid was cooled to 25° by placing in cold water, the sodium methylate solution poured in, stirred, and immediately 40 ml of methyl iodide added. The reaction mixture was heated with reflux condenser on a water bath (70-72°) until it boiled gently for 10 hours After cooling, the solution was filtered from the sediment and methanol evaporated off until volume of the residue was 250 ml. To the residue was added 165 ml of aqueous methylamine solution of concentration 0.54 g/ml. After several minutes a white precipitate of dimethyldiamide settled out and was left overnight to crystallize. Weight of dried product 75.25 g (70.65% calculated on initial ester of imidazole-4,5-dicarboxylic acid). For purification, the substance was recrystallized three times from water, the first time using carbon. The mother liquors obtained during recrystallizations were concentrated by evaporation, and the dimethylamide obtained from them after similar purification added to the main product. Yield of purified compound 60 g (56.33%). Antifeine took the form of white crystals with m.p. 194-195°.

Found %: N 28.67; C 48.95; H 6.09. $C_8H_{12}O_2N_4$. Calculated %: N 28.55; C 48.97; H 6.17.

Method B. 20 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid was dissolved in 900 ml of anhydrous methanol by boiling and stirring for ~15 minutes. A sodium methylate solution in methanol was prepared separately by placing 2.7 g of sodium in 75 ml of methanol. The solution of the ester in methanol was cooled to 25°, the sodium methylate solution poured in and, bubbling a continuous stream of methyl bromide, the reaction mixture was boiled on a water bath for 9 hours using a reflux condenser with dry ice. Total amount of methyl bromide passed after this period of time amounted to about a 10 fold excess of that theoretically necessary. On completion of alkylation, evaporation of methanol was carried out, and precipitation and purification of antifeine in a similar manner to that indicated in "method A." Yield of purified antifeine 52-54%.

Quantitative determination of antifeine. An accurately weighed sample of about 0.25 g of the compound was placed in a 500 ml round-bottomed flask, 200 ml of distilled water poured in and the flask fitted to a Kjeldahl apparatus for ammonia distillation [13]. In the receiver was placed 40 ml of 0.1 N sulfuric acid solution. Through the funnel of the apparatus was added 40 ml of 40% caustic soda solution and, heating the reaction mixture, distillation of methylamine into sulfuric acid carried out. On completing the distillation, remaining free sulfuric acid was back-titrated. A blank experiment was carried out under these conditions. Antifiene found 99.6%.

1-Methylimidazole-4,5-dicarboxylic acid. To prove the structure of antifeine it was converted into 1-methylimidazole-4,5-carboxylic acid. To do this, 1 g of antifeine was boiled for 1 hour with 50 ml of 20% caustic potash in a flask with reflux condenser. The hot solution was acidified with dilute (1 : 1) hydrochloric acid (40 ml), cooled and filtered. The precipitate was washed with 25 ml of ice water and dried at 100° for 1 hour. Melting point of the 1-methylimidazole-4,5-dicarboxylic acid 262-263°. According to the data in the literature [15] the acid melts at 261-262°.

SUMMARY

1. Synthesis was achieved of the dimethyl-, diethyl-, and dibutyldiamides of imidazole-4,5-dicarboxylic acid, and also of the dimethyldiamide of 1-methylimidazole-4,5-dicarboxylic acid (antifeine). These compounds can be regarded as "open" structural analogs of xanthine derivatives, in the pyrimidine ring of which the nitrogen and carbon atoms are rearranged together with their substituents. The first three compounds possess a stimulating action on the central nervous system, antifeine, however, displaying the properties of a caffeine antagonist and having therapeutic value as a sedative (tranquilizing) agent.

2. A method for quantitative analysis of antifeine was worked out.

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DERIVATIVES OF IMIDAZOLE DICARBOXYLIC ACIDS

II. DIMETHYLDIAMIDES OF 1-ALKYLIMIDAZOLE-4,5-DICARBOXYLIC ACIDS

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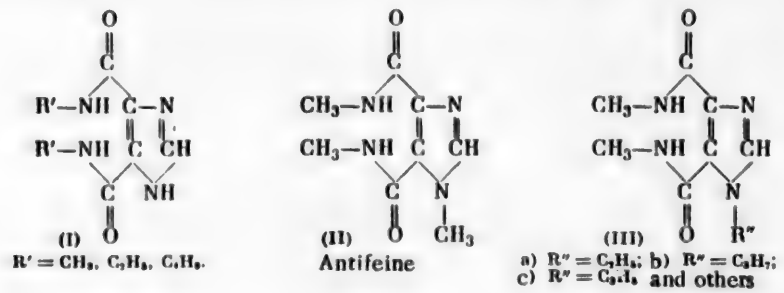
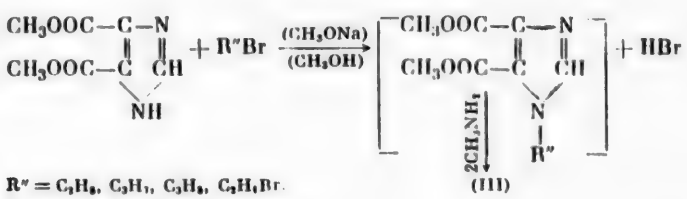
Original article submitted June 2, 1960

In a previous communication [1] synthesis was described of three dialkyldiamides of imidazole-4,5-dicarboxylic acid (I) and of the dimethyldiamide of 1-methylimidazole-4,5-dicarboxylic acid or "antifeine" (II).



Pharmacological investigation of the compounds obtained showed that compounds of type (I) possess a stimulating action, while antifeine (II) exhibits sedative, i.e., tranquilizing properties [2]. In view of the fact that antifeine is a medicinal preparation having therapeutic use, further synthesis of antifeine analogs of general formula (III) has been undertaken.

Synthesis was achieved using the dimethyl ester of imidazole-4,5-dicarboxylic acid, which was alkylated with alkyl bromides in a methanol solution of sodium methylate. The resulting esters were not isolated from the reaction mixture, but immediately converted into dimethyldiamides by the action of aqueous methylamine solutions, according to the scheme

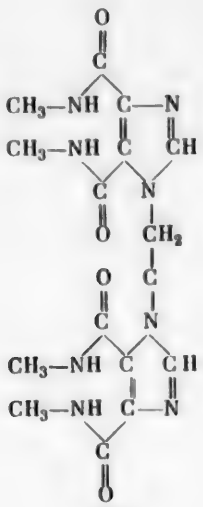


The following dimethyldiamides were prepared: those of 1-ethylimidazole-4,5-dicarboxylic acid or "ethylnorantifeine" (IIIb), 1-allylimidazole-4,5-dicarboxylic acid or "allylnorantifeine" (IIIc), 1-benzylimidazole-4,5-dicarboxylic acid or "benzylnorantifeine" (IIId), and the tetramethyltetraamide of bisimidazolylethanetetracarboxylic acid or "diantifeine" (IIIe).

In the preparation of antifeine, alkylation of the ester of imidazole-4,5-dicarboxylic acid was achieved with both methyl iodide and bromide, antifeine yield being the same in both cases [1]. In the preparation of ethyl-

norantifeine, however, better yields were achieved by using ethyl bromide, used in excess (200%). In the preparation of the remaining dimethyldiamides of 1-alkylimidazole-4,5-dicarboxylic acids, alkyl bromides were employed exclusively, used in 100% excess.

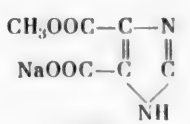
It should be noted that while antifeine (II) crystallized readily on reacting methylamine with the ester solutions resulting from alkylation, its latter analogs (III) precipitated as gelatinous gels which were complex mixtures, thus making the work difficult. To prepare dimethyldiamides (IIIa-IIId) a solution of the gels obtained by addition of water was used, followed by extraction of the solution with chloroform. After evaporation of the chloroform extracts on a water bath, solid precipitates were obtained, which were purified by three recrystallizations from water, the first time with addition of activated carbon. Yields of the dimethyldiamides thus purified (IIIa-IIId) amounted to ~18-39%, calculated on initial ester of imidazole-4,5-dicarboxylic acid. Investigation showed that the method worked out by us previously [1] for quantitative analysis of antifeine and applicable to industrial production, was also of use in the case of ethylnorantifeine.



(IIId)

The tetramethyltetraamide of bisimidazolylethanetetracarboxylic acid (IIIe) was prepared with a yield of only ~9%, the main reaction product being the previously described dimethyldiamide of imidazole-4,5-dicarboxylic acid [1]. This indicates that only slight alkylation of the ester of imidazole-4,5-dicarboxylic acid with dibromoethane is takes place.

While preparing the initial ester of imidazole-4,5-dicarboxylic acid by esterification according to the method of Baxter [3] it was noticed that in most cases the reaction does not proceed fully to completion. From the concentrated mother liquor after separation of the crystalline dimethyl ester of imidazole-4,5-dicarboxylic acid the sodium salt of the monoester of imidazole-4,5-dicarboxylic acid (IV) was obtained, this salt being previously not described in the literature. This substance was characterized by quantitative conversion into imidazole-4,5-dicarboxylic acid, which is very poorly soluble in water. For use in preparing the dimethyl ester of imidazole-4,5-dicarboxylic acid the sodium salt



(IV)

of the monoester was dissolved in water, the solution acidified and the precipitated ester-acid subjected to the usual esterification in a stream of hydrogen chloride. The dimethyl ester of imidazole-4,5-dicarboxylic acid thus synthesized was identified with a sample of the ester obtained by direct esterification of the acid.

Pharmacological study of the preparations obtained* showed that all the dimethyldiamides of the imidazole-4,5-dicarboxylic acids with substituents in the first position of the imidazole ring possess a sedative, i.e., tranquilizing action on the central nervous system [4]. In the case of preparations (III a, b, c, d) this action is considerably stronger than for antifeine, preparation (IIIe) being characterized by a weaker sedative action than antifeine.

EXPERIMENTAL

Imidazole-4,5-dicarboxylic acid was prepared by oxidizing benzimidazole in a sulfuric acid medium, as described previously [1].

Dimethyl ester of imidazole-4,5-dicarboxylic acid was prepared starting from 40 g of imidazole-4,5-dicarboxylic acid, with a yield of ~52% [1].

Sodium salt of monomethyl ester of imidazole-4,5-dicarboxylic acid (IV). The mother liquor obtained after filtration of the unpurified ester synthesized from 40 g of imidazole-4,5-dicarboxylic acid by the method described previously [1] was concentrated by evaporation to a volume of 350 ml. On cooling the solution, crystals were obtained of the esterification by-product, the sodium salt of the monoester of imidazole-4,5-dicarboxylic acid, in amount 22 g (44.6%, calculated on initial acid). A sample for analysis was boiled with methanol to extract possible traces of the ester of imidazole-4,5-dicarboxylic acid, and recrystallized three times from water. The substance did not melt up to 300°.

Found %: Na 11.67. $C_6H_5O_4N_2Na$. Calculated %: Na 11.9.

For conversion into imidazole-4,5-dicarboxylic acid a sample of 1.0036 g of the sodium salt was boiled with 25 ml of 25% caustic potash solution for 0.5 hours, and the hot solution precipitated with hydrochloric acid. The precipitate obtained was filtered off and washed for a considerable time with distilled water. Yield of imidazole-4,5-dicarboxylic acid was 0.766 g (99.8%). M.p. ~290° (with decomp.). According to the data in the literature [5] imidazole-4,5-dicarboxylic acid melts at 288°.

Found %: N 17.33. $C_5H_4O_4N_2$. Calculated %: N 17.94.

With the aim of using the sodium salt of the monester for conversion into the diester of imidazole-4,5-dicarboxylic acid, the following method was employed: 70 g of dry sodium salt was dissolved in 600 ml of water by boiling, the hot solution acidified with hydrochloric acid until acid to congo and the precipitated ester-acid filtered off after cooling the solution (the filtrate was concentrated to obtain additional amounts of ester-acid). Yield of ester-acid 44.1 g (71.2%). Then 39.55 g of the ester-acid thus prepared was esterified with methanol by boiling with reflux condenser and bubbling a vigorous stream of hydrogen chloride until the ester-acid precipitate dissolved. The reaction mixture was neutralized with saturated soda solution to pH 6-7 and acidified with acetic acid to pH 4. The precipitated diester was recrystallized from hot water. Yield 28 g (65%, calculated on initial ester-acid). M.p. 202-203°. A sample mixed with an authentic sample of the dimethyl ester of imidazole-4,5-dicarboxylic acid showed no melting point depression. According to the data in the literature the ester melts at 200-203° [3].

Dimethyldiamide of 1-ethylimidazole-4,5-dicarboxylic acid or "Ethylnorantifeine" (IIIa). The preparation was obtained starting from 20 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid. The entire alkylation procedure and proportions of reagents used, except of alkyl halide, were completely identical to those given in the "method A" section for antifeine [1]. Instead of methyl iodide, ethyl bromide was used, which in 100% excess was poured after the sodium methylate solution into a cold solution of the dimethyl ester of imidazole-4,5-dicarboxylic acid. The reaction mixture was gently boiled for ~10 hours at water bath temperature 67-68°, the solution then cooled to 25°, 100% excess of ethyl bromide poured in and the mixture boiled for a further 6 hours. After methanol evaporation, to the indigo residue (~50 ml) was added 33 ml of aqueous methylamine solution with a concentration of 0.54 g/ml. In most cases ethylnorantifeine precipitated from solution as a gelatinous mass after several hours or on another day. To obtain the pure substance the following method was used. To the reaction mixture was added 100 ml of water, 100 ml of chloroform and heated with reflux condenser on a water bath for 5-10 minutes until boiling, the precipitate of gel then dissolving completely. The layers were separated in a separatory funnel and similar extraction with chloroform repeated a further two times (with 75 ml amounts of chloroform). The chloroform extracts were united and evaporated to dryness on a water bath. Weight of dry residue 19.71 g. The product was recrystallized three times from water, the first time using activated carbon. Weight of purified ethylnorantifeine 8.97 g (43.8%, calculated on initial ester of imidazole-4,5-dicarboxylic acid). White crystals with m.p. 142-143°.

Found %: N 26.63; C 51.26; H 6.85. $C_9H_{14}O_2N_4$. Calculated %: N 26.65; C 51.41; H 6.71.

* The study of the pharmacological properties of all the compounds obtained was carried out by Yu. S. Borodkin.

Quantitative determination of ethylnorantifeine was achieved by the method described for antifeine [1]. Ethylnorantifeine found, 99.5%.

Dimethyldiamide of 1-propylimidazole-4,5-dicarboxylic acid or "Propylnorantifeine" (IIIb). Synthesis of the preparation was achieved starting from 20 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid in a similar manner to that described in the section "method A" for antifeine [1]. Instead of methyl iodide, after sodium methylate propyl bromide in 100% excess was added to the cold solution of the ester. The reaction mixture was boiled for 10 hours on a water bath at 70-72°. Further treatment of the reaction mixture was completed identical to that carried out for ethylnorantifeine. After adding the methylamine solution a very small amount of a gelatinous precipitate formed; most of the propylnorantifeine remained in solution. Yield of purified propylnorantifeine 4.5 g (18%, calculated on initial ester of imidazole-4,5-dicarboxylic acid). White crystals with m.p. 86-87°, readily soluble in water.

Found %: N 24.70; C 53.82; H 7.20. $C_{10}H_{16}O_2N_4$. Calculated %: N 24.98; C 53.55; H 7.19.

Besides propylnorantifeine, from the reaction mixture was isolated a small amount of the dimethyldiamide of imidazole-4,5-dicarboxylic acid, described previously [1].

Dimethyldiamide of 1-allylimidazole-4,5-dicarboxylic acid or "Allylnorantifeine" (IIIc). Synthesis of the preparation was achieved starting from 40 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid, in manner completely similar to synthesis of antifeine [1], instead of methyl iodide allyl bromide being used in 100% excess, added immediately after the sodium methylate. After adding methylamine to the concentrated solution of alkylated ester a gelatinous precipitate was obtained. The complete reaction mixture was treated with chloroform, in a manner similar to that described for ethylnorantifeine. Weight of dry residue obtained after concentrating the united chloroform extracts 30 g. The substance was purified by recrystallizing three times from water (the first time with carbon). It formed white crystals, readily soluble in water. Yield 15 g (31.25%, calculated on initial ester of imidazole-4,5-dicarboxylic acid). M.p. 91-93°.

Found %: N 25.54; C 54.17; H 6.35. $C_{10}H_{14}O_2N_4$. Calculated %: N 25.21; C 54.03; H 6.34.

Dimethyldiamide of 1-benzylimidazole-4,5-dicarboxylic acid or "benzylnorantifeine" (IIId). The preparation was prepared similarly to the foregoing, starting from 40 g of the ester of imidazole-4,5-dicarboxylic acid and 100% excess benzyl bromide. The product precipitated as a gelatinous gel. After treatment with chloroform the substance was recrystallized three times from large amounts of water. The preparation was very poorly soluble in water. Yield 20%, calculated on initial ester of imidazole-4,5-dicarboxylic acid. M.p. 110-111°.

Found %: N 20.94; C 61.90; H 6.15. $C_{14}H_{16}O_2N_2$. Calculated %: N 20.57; C 61.75; H 5.92.

Tetramethyltetraamide of bis-imidazolylethanetetracarboxylic acid or "Diantifeine" (IIIe). Synthesis of the preparation was achieved starting from 40 g of the dimethyl ester of imidazole-4,5-dicarboxylic acid, similarly to the synthesis of antifeine [1], instead of methyl iodide,dibromoethane in 100% excess being used, added immediately after the sodium methylate. Further treatment of the reaction mixture was similar to that used in antifeine synthesis [1]. After evaporation of methanol from the solution obtained as a result of alkylation, a gelatinous mass of esters formed, which was dissolved in water or methanol with heating, filtered from undissolved impurities and the filtrate precipitated with methylamine solution. On standing the reaction solution for 1-2 days a small amount of white crystals precipitated, poorly soluble in water and alcohol. The substance was purified by three recrystallizations from alcohol. Yield 3.72 g (8.7%), calculated on initial ester of imidazole-4,5-dicarboxylic acid. M.p. 256-257°.

Found %: N 28.77; C 49.32; H 5.85. $C_{16}H_{22}O_4N_8$. Calculated %: N 28.70; C 49.22; H 5.68.

After separation of tetramethyltetraamide, the filtrate was concentrated on a water bath until crystallization began, the solution then cooled and the substance precipitating out filtered off. After three recrystallizations the preparation obtained melted at 221° and gave no melting point depression with the authentic dimethyldiamide of imidazole-4,5-dicarboxylic acid. Yield 8 g (20.3%, calculated on initial ester).

SUMMARY

1. Synthesis was achieved of the dimethyldiamides of 1-ethyl-,1-propyl-, 1-allyl-, and 1-benzylimidazole-4,5-dicarboxylic acids and of the tetramethyltetraamide of bisimidazolylethanetetracarboxylic acid. All the preparations obtained have a tranquilizing effect on the central nervous system. The first four compounds are highly active pharmacologically, the latter compound slightly active.

2. For the first time, the sodium salt of the monomethyl ester of imidazole-4,5-dicarboxylic acid was prepared, and was converted for proof of its structure into imidazole-4,5-dicarboxylic acid and into the dimethyl ester of imidazole-4,5-dicarboxylic acid.

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DERIVATIVES OF IMIDAZOLE DICARBOXYLIC ACIDS

III. DIMETHYLDIAMIDES OF 2-ALKYLIMIDAZOLE-4,5-DICARBOXYLIC ACIDS

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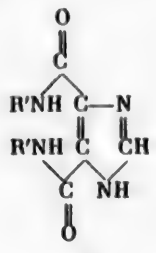
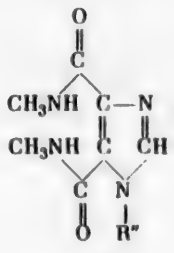
Original article submitted June 2, 1960

In previous communications [1, 2] synthesis was described of dialkyldiamides of imidazole-4,5-dicarboxylic acid (I) and of dimethyldiamides of 1-alkylimidazole-4,5-dicarboxylic acids (II). Pharmacological investigation showed that compounds (I) with unsubstituted 1 and 2 positions in the imidazole ring are stimulators of the central nervous system [3, 4], and that compounds (II) having substituents in the first position of the imidazole rings possess a sedative, i.e., tranquilizing, action [3, 4].

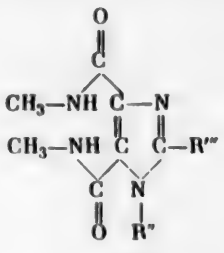
Substances similar in structure and substituted at the second carbon atom of the imidazole ring (III) have not been prepared up till now, and so synthesis and study of the physiological action of such compounds presented considerable interest.



(I)
R′ = CH_3, C_2H_5, C_3H_7

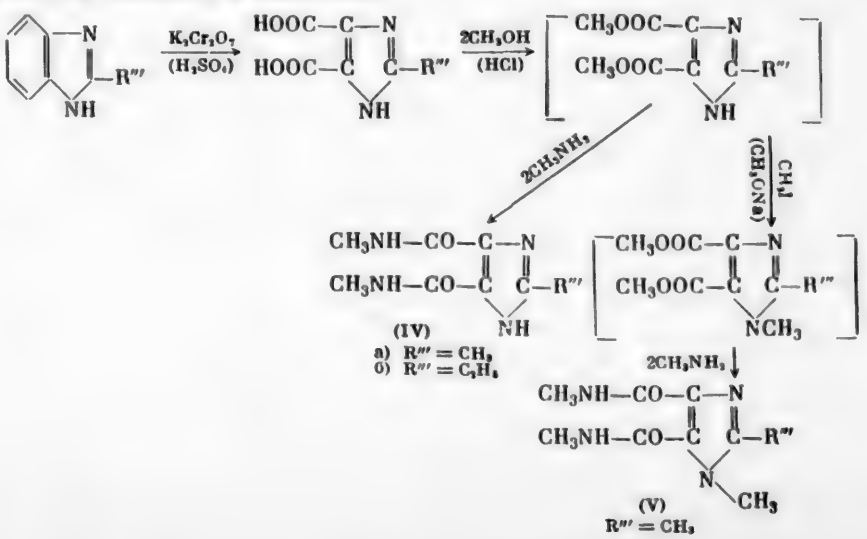


(II)
R″ = CH_3, C_2H_5, C_3H_7, etc.



(III)
R″ = H, CH_3, R‴ = CH_3, C_2H_5.

Initial substances in preparation of preparations of type (III) were 2-methyl- and 2-ethylimidazole-4,5-dicarboxylic acids, obtained by oxidation of the corresponding benzimidazoles with potassium bichromate in sulfuric acid medium [5]. The acids were esterified with methanol in a stream of hydrogen chloride, and the resulting ester solutions after neutralization and concentration used for preparation of dimethyldiamides (IV). Yield of the latter amounted to 33-53%, calculated on initial acids.



(IV)
a) R‴ = CH_3
b) R‴ = C_2H_5

(V)
R‴ = CH_3

To prepare dimethyldiamide (V) the dry ester of 1,2-dimethyldimidazole-4,5-dicarboxylic acid (mixed with inorganic salts) was alkylated with methyl iodide in presence of sodium methylate by the method of Baxter [6] and then converted into dimethyldiamide (V) by the action of aqueous methylamine solution. Yield of dimethyldiamide (V) amounted to 27%. As a by-product in this synthesis the dimethyldiamide of 2-methylimidazole-4,5-dicarboxylic acid (IVa) described above was obtained in ~12% yield.

Pharmacological study of preparations (IVa, b) and (V) showed that their activity is considerably lower than that of the derivatives of imidazole-4,5-dicarboxylic acids synthesized previously [1, 2]. Compounds (IVa, b) and (V) are capable of lowering brain cortex tone slightly only in large doses [4]. From the above it can be concluded that in the search for new substances with a sedative (i.e., tranquilizing) action in the series of the dimethyldiamides of imidazole-4,5-dicarboxylic acids, substituents in position-2 of the imidazole ring should be introduced.

EXPERIMENTAL

2-Methyl- and 2-ethylimidazole-4,5-dicarboxylic acids were prepared from 2-methyl- and 2-ethylbenzimidazoles [5]. For purification the acids were reprecipitated from a hot ammoniacal solution of their ammonia salts with hydrochloric acid, then the mother liquors obtained after separation of the acids concentrated by evaporation to a volume of ~100 ml to obtain full yields of the purified acids. Yields of purified acids amounted to 35 and 19.5% respectively.

Dimethyldiamide of 2-methylimidazole-4,5-dicarboxylic acid (IVa). 20 g of 2-methylimidazole-4,5-dicarboxylic acid was esterified with methanol in a stream of hydrogen chloride with gentle boiling of the methanol. Esterfication was continued for a further 3 hours after solution of the acid precipitate. The reaction mixture was neutralized with saturated aqueous sodium carbonate solution and concentrated on a water bath to volume of ~185 ml. A precipitate of the sodium salt of 2-methylimidazole-4,5-dicarboxylic acid (3.7 g) separated out, from which after solution in a small volume of water 2-methylimidazole-4,5-dicarboxylic acid (3.5 g) was regenerated by acidification with hydrochloric acid. The filtrate, after separation of the sodium salt of the acid, was used for preparation of dimethyldiamide (IVa). On adding 140 ml of 20% aqueous methylamine solution a white precipitate of dimethyldiamide immediately separated out, was filtered off and recrystallized three times from water (the first time using carbon). Weight of product 2.2 g. M.p. 225-226°. From the mother liquor containing excess methylamine, by adding concentrated hydrochloric acid to pH 4, was obtained an additional amount of dimethyldiamide (IVa). M.p. 225-226°. A sample mixed with the dimethyldiamide precipitated from alkaline solution showed no melting point depression. Total yield of purified dimethyldiamide (IVa) 10.2 g (54%, calculated on reacted acid).

Found %: N 28.78; C 49.18; H 6.1. $C_8H_{12}O_2N_4$. Calculated %: N 28.55; C 48.97; H 6.17.

Dimethyldiamide of 2-ethylimidazole-4,5-dicarboxylic acid (IVb). 6 g of 2-ethylimidazole-4,5-dicarboxylic acid was esterified with methanol in a stream of hydrogen chloride. Esterification was continued for a further 4 hours after the acid began to dissolve. The reaction mixture was neutralized with soda solution to pH 4 and concentrated on a water bath to a volume of 60 ml. The precipitate of salts settling out was filtered off without regeneration from its acid. To the filtrate was added 30 ml of 20% methylamine solution. On the following day excess methylamine was neutralized with concentrated hydrochloric acid on cooling, a white precipitate of dimethyldiamide (IVb) settling out. Yield 2.3 g (33.62%, calculated on initial acid). The product was recrystallized three times from water. M.p. 221-22°.

Found %: N 26.74; C 51.59; H 6.91. $C_9H_{14}O_2N_4$. Calculated %: N 26.65; C 51.41; H 6.71.

Dimethyldiamide of 1,2-dimethylimidazole-4,5-dicarboxylic acid (V). 31.7 g of 2-methylimidazole-4,5-dicarboxylic acid was esterified in a stream of hydrogen chloride with methanol until the acid precipitate dissolved and then for a further 3 hours. The reaction mixture was neutralized with soda solution and acidified with acetic acid to pH 4. The solution was concentrated on a water bath, a precipitate of the sodium salt of 2-methylimidazole-4,5-dicarboxylic acid settling out, which was dissolved in 100 ml of water, acidified and concentrated to small volume. 7.77 g of 2-methylimidazole-4,5-dicarboxylic acid was regenerated. The filtrate after separation of the sodium salt was distilled in vacuo at 20 mm to remove water. The residue was dried at 100°, ground and transferred to a flask, to which was added 1 liter of dry methanol, 3.2 g metallic sodium, and 10.4 ml of methyl iodide. The reaction mixture was heated with mixing with a stirrer and gentle boiling on a water bath with reflux condenser for 10 hours. After filtration from inorganic impurities and evaporation of methanol to the indigo residue (~ 50 ml) was added 60 ml of aqueous methylamine with a concentration of 0.3 g/ml. On the following day a white precipitate of the dimethyldiamide of 1,2-dimethylimidazole-4,5-dicarboxylic acid (V) separated out, m.p. 170-193°. Yield

7.95 g (26.87% on reacted acid). After three recrystallizations from water (the first time with carbon) 2.8 g of purified preparation was obtained as white crystals with m.p. 191.5-192.5°.

Found %: N 26.85; C 51.20; H 6.93. $C_9H_{14}O_2N_4$. Calculated %: N 26.65; C 51.41; H 6.71.

From the mother liquor, containing excess methylamine, after neutralization with hydrochloric acid to pH 4 and concentration on a water bath, 3.34 g of the dimethyldiamide of 2-methylimidazole-4,5-dicarboxylic acid (IVa) was obtained (yield 12.1% on reacted acid). M.p. 225-226°. A sample mixed with authentic dimethyldiamide of 2-methylimidazole-4,5-dicarboxylic acid showed no melting point depression.

Found %: N 28.85. $C_8H_{12}O_2N_4$. Calculated %: N 28.55.

SUMMARY

Synthesis was accomplished of the dimethyldiamides of 2-methyl- and 2-ethylimidazole-4,5-dicarboxylic acids and of 1,2-dimethylimidazole-4,5-dicarboxylic acids and of 1,2-dimethylimidazole-4,5-dicarboxylic acid.

The compounds obtained possess slight sedative action, evident only on using large doses of these preparations.

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INVESTIGATIONS IN THE FIELD OF THE 2-(β- AND γ-PYRIDYL)-Δ^2-THIAZOLINES

II. SYNTHESIS OF 2-(α-ALKYL-γ-PYRIDYL)-Δ^2-THIAZOLINES, THEIR 4-CARBOXYLIC ACIDS, AND OF (β- AND γ-PYRIDYL)-2-THIAZOLYL-Δ^2-METHANES

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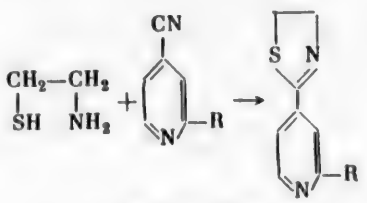
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 5, pp. 1479-1483, May, 1961
Original article submitted May 23, 1960

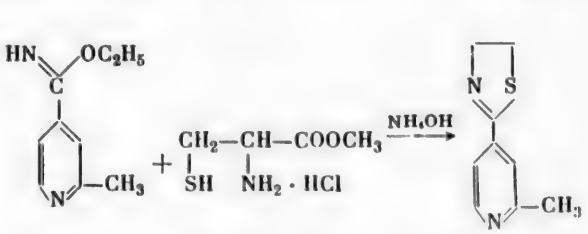
In a previous article [1] we described the preparation of 2-(β- and γ-pyridyl)-Δ^2-thiazolines and their 4-carboxylic acids. These compounds appeared to possess some tuberculostatic activity. It appeared expedient to attempt to increase this activity by introducing alkyl groups into the α-position of the pyridine nucleus, which step is known to be favorable in the case of 4-pyridylthiocarbamides [2]. It should be noted also that the 2-benzyl- and 2-naphthyl-Δ^2-thiazolines and α-phenyl-β-thiazolinyl-2-ethylene derivatives described in the literature [3] showed antibacterial (including antitubercular) action, and also pharmacological activity with slight toxicity. Thus it was of interest to synthesize similar thiazolines with pyridine substituents.

Synthesis of a thiazoline ring in position 4 of the pyridine ring was achieved by us by reacting the corresponding nitriles [4] and cysteamine [3].

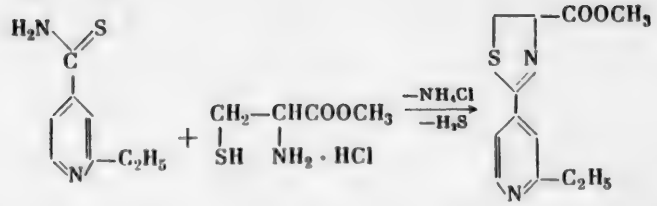


R = CH_3, C_4H_9.

The methyl ester of 2-(α-methyl-γ-pyridyl)-Δ^2-thiazoline-4-carboxylic acid was synthesized from the iminoester of α-methyl-γ-pyridylcarboxylic acid and the hydrochloride of the methyl ester of cysteine [5].



The methyl ester of 2-(α-ethyl-γ-pyridyl)-Δ^2-thiazoline-4-carboxylic acid was synthesized from α-methyl-γ-pyridylthioamide and the hydrochloride of the cysteine ester [6] according to a similar scheme.



We also synthesized similar compounds in which β- and γ-pyridine and Δ^2-thiazoline residues were linked via methylene group. Initial substances were γ-(cyanomethyl)- and β-(cyanomethyl)-pyridines, from which for the first time 4-(cyanomethyl)-pyridine was obtained by us.

We varied somewhat the method of synthesis of β-(cyanomethyl)-pyridine [7] and increased yield from 35 to 61%. From these compounds by the action of hydrogen sulfide in presence of triethylamine in alcoholic solution thiomides were obtained which are also of interest in tuberculostatic investigation.

EXPERIMENTAL

2-(α-Methyl-γ-pyridyl)-Δ^2-thiazoline (I). A solution of 1.54 g of cysteamine and 2.95 g of α-methyl-γ-cyanopyridine in 15 ml of anhydrous alcohol saturated with nitrogen was boiled with stirring in a stream of nitrogen for 7 hours (until a negative reaction was obtained with sodium nitroprusside on the free mercapto-group and evolution of ammonia ceased). After completion of the reaction, solvent was removed in vacuo, the residue distilled, and a fraction collected at 113-114° (0.6 mm). 2.64 g (74.2%) of a colorless oil was obtained, soluble in organic solvents, insoluble in water. The substance purified via the crystallized salicylate. M.p. 37-39°.

Found %: C 60.27; H 5.63; N 16.30; S 18.23. $C_9H_{10}N_2S$. Calculated %: C 60.62; H 5.65; N 15.78; S 18.02.

The salicylate was prepared in quantitative yield by the action of a 2 N alcoholic solution of salicylic acid. Colorless needles from 50% alcohol, readily soluble in organic solvents, sparingly in water. M.p. 77-78°.

Found %: C 60.95; H 5.28; N 8.96; S 9.74. $C_9H_{10}N_2S \cdot C_7H_6O_3$. Calculated %: C 60.80; H 5.09; N 8.84; S 10.11.

The picrate was prepared in alcohol solution. Yellow prisms (from acetone). M.p. 203-204° (decomp.).

Found %: C 44.46; H 2.98; N 16.60; S 7.57. $C_9H_{10}N_2S \cdot C_6H_3O_7N_3$. Calculated %: C 44.81; H 3.21; N 17.19; S 7.89.

2-(α-Butyl-γ-pyridyl)-Δ^2-thiazoline (II). The reaction was carried out similarly to that described above by reacting 0.77 g of cysteamine and 1.93 g of α-butyl-γ-cyanopyridine in 15 ml of anhydrous alcohol. The residue was distilled in vacuo. The fraction boiling at 165-168° (1.3 mm) was a colorless oil, soluble in organic solvents, insoluble in water. Yield 1.39 g (62%).

Found %: C 65.62; H 7.38; N 12.84; S 14.17. $C_{12}H_{16}N_2S$. Calculated %: C 65.42; H 7.32; N 12.71; S 14.16.

The salicylate was soluble in organic solvents, with difficulty in water. Colorless prisms from 50% alcohol. M.p. 79-80°.

Found %: C 63.73; H 6.11; N 7.81; S 8.94. $C_{12}H_{16}N_2S \cdot C_7H_6O_3$. Calculated %: C 63.70; H 6.19; N 7.81; S 8.95.

The picrate was obtained as light-yellow crystals from alcohol. M.p. 120-121°.

Found %: C 48.19; H 4.20; N 15.23; S 7.06. $C_{12}H_{16}N_2S \cdot C_6H_3O_7N_3$. Calculated %: C 48.11; H 4.27; N 15.19; S 7.17.

Methyl ester of 2-(α-methyl-γ-pyridyl)-Δ^2-thiazoline-4-carboxylic acid (III). The hydrochloride of the methyl ester of cysteine [4], obtained from 3.12 g of cysteine, was dissolved in 6 ml of distilled water saturated with nitrogen, and the solution neutralized with concentrated ammonia to pH 3. To it was added a solution of the imino ester of α-methyl-γ-pyridylcarboxylic acid (synthesized similarly to the imino ester of γ-pyridylcarboxylic acid from 3.54 g of α-methyl-γ-cyanopyridine) in 20 ml of ether. The reaction mixture was stirred at room temperature for 30 hours. The ethereal layer was then separated, the aqueous extracted with ether, the extract dried with magnesium sulfate with addition of carbon. After removal of solvent from the oily residue decomposing on distillation in vacuo, the salicylate was obtained.

Colorless crystals (from 50% alcohol), readily soluble in organic solvents, with difficulty in water. M.p. 121.5-122°.

Found %: C 57.88; H 4.51; N 7.56; S 8.80. $C_{11}H_{12}O_2N_2S \cdot C_7H_6O_3$. Calculated %: C 57.74; H 4.84; N 7.48; S 8.56.

Methyl ester of 2-(α-ethyl-γ-pyridyl)-Δ^2-thiazoline-4-carboxylic acid (IV). 1.71 g of the hydrochloride of the methyl ester of cysteine and 2 g of α-ethyl-γ-pyridylthioamide were heated for 2 hours at 120° with stirring. The reaction mixture melted and darkened; hydrogen sulfide evolution was observed. The oily mixture was extracted with ether.

The salicylate was obtained after removal of solvent from the oily residue. Colorless prisms (from alcohol), readily soluble in organic solvents, with difficulty in water. M.p. 146-147°.

Found %: C 59.09; H 4.86; N 7.30; S 8.58. $C_{12}H_{14}O_2N_2S \cdot C_7H_6O_3$. Calculated %: C 58.70; H 5.18; N 7.22; S 8.27.

γ-(Cyanomethyl)-pyridine (V). 5.21 g of the amide of γ-pyridylacetic acid [6] was heated with stirring with 18 ml of freshly distilled phosphorus oxychloride at 120-125°. The reaction mixture gradually darkened. After 6 hours the phosphorus oxychloride remaining was removed in vacuo, adding benzene twice. After cooling, the brown mass was gradually transferred to a mixture of water and ice. The resulting solution was rendered alkaline with 50% caustic potash to pH 8 and extracted with ether. After drying with magnesium sulfate with addition of carbon and removal of solvent in vacuo, the residue crystallized. Colorless crystals were obtained from a mixture of ether and petroleum ether, readily soluble in organic solvents, insoluble in water. On storage, the substance became rose-colored. M.p. 43-44°. Yield 2.65 g (58.5%).

Found %: C 71.53; H 5.15; N 23.64. $C_7H_6N_2$. Calculated %: C 71.20; H 5.11; N 23.72.

γ-Pyridyl-2-Δ^2-thiazolinylmethane (VI). Synthesis was carried out similarly to (I) from 3 g of (V) and 2.31 g of cysteamine in 20 ml of anhydrous alcohol. After removal of solvent in vacuo, the residue was distilled. B.p. 138-139° (0.6 mm). 2.6 g (57%) of an oily substance was obtained, soluble in organic solvents, insoluble in water.

The hydrochloride was obtained by the action of alcoholic hydrogen chloride solution. Colorless crystals from methyl alcohol, readily soluble in water and alcohols, insoluble in organic solvents. M.p. 193-195° (decomp.).

Found %: C 43.75; H 4.93; N 11.11; S 12.10; Cl 28.50. $C_9H_{10}N_2S \cdot 2HCl$. Calculated %: C 43.15; H 4.82; N 11.14; S 12.76; Cl 28.21.

Picrate—yellow crystals (from 50% alcohol). M.p. 169-170° (decomp.).

Found %: N 17.17. $C_9H_{10}N_2S \cdot C_6H_3O_7N_3$. Calculated %: N 17.19.

β-Pyridyl-2-Δ^2-thiazolinylmethane (VII) was obtained similarly to (I) from 1.93 g of cysteamine and 2.6 g of β-(cyanomethyl)-pyridine [synthesized by us, as for (V), in 61% yield] in 10 ml of anhydrous alcohol. B.p. 137-140° (0.4 mm). Yield 2.54 g (65%) of a colorless oil, soluble in organic solvents, insoluble in water.

Hydrochloride—colorless crystals from methyl alcohol, readily soluble in water and alcohols, insoluble in organic solvents. M.p. 214-215°.

Found %: C 43.21; H 4.80; N 10.96; S 12.80; Cl 28.36. $C_9H_{10}N_2S \cdot {}_2HCl$. Calculated %: C 43.15; H 4.82; H 11.14; S 12.76; Cl 28.21.

Picrate—yellow crystals from acetone. M.p. 192-193°.

Found %: N 17.56. $C_9H_{10}N_2S \cdot C_6H_3O_7N_3$. Calculated %: N 17.19.

Thioamide of γ-pyridylacetic acid (VIII). Dry hydrogen sulfide was bubbled for 3 hours into a solution of 2.36 g of (V) and 2 ml of triethylamine in 10 ml of anhydrous alcohol at room temperature. The reaction mixture was then left overnight in a sealed flask. The substance crystallized on cooling. Yield 2.73 g (77.5%). Colorless prisms from alcohol, readily soluble in alcohols, acetone, ethyl acetate, sparingly in water. M.p. 168-169° (decomp.).

Found %: C 55.13; H 5.30; N 18.34; S 20.89. $C_7H_8N_2S$. Calculated %: C 55.20; H 5.29; N 18.38; S 21.07.

Thioamide of β-pyridylacetic acid (IX). Obtained similarly to (VIII) from 2 g of β-(cyanomethyl)-pyridine in presence of 1 ml triethylamine in 10 ml of anhydrous alcohol. Yield 1.9 g (74%). Colorless prisms from alcohol, readily soluble in alcohols, acetone, ethyl acetate, sparingly in water. M.p. 135-136.5°.

Found %: C 55.18; H 5.36; N 18.30; S 20.74. $C_7H_8N_2S$. Calculated %: C 55.20; H 5.29; N 18.38; S 21.07.

SUMMARY

1. By condensing α-methyl- and α-butyl-γ-cyanopyridines with cysteamine the corresponding 2-(α-methyl-γ-pyridyl)- and 2-(α-butyl-γ-pyridyl)-Δ^2-thiazolines were obtained.

2. By condensing the methyl ester of cysteine with the imino ester of α-methyl-γ-pyridylcarboxylic acid the methyl ester of 2-(α-methyl-γ-pyridyl)-Δ^2-thiazoline-4-carboxylic acid was synthesized.

3. By reacting α-ethyl-γ-pyridylthioamide with the hydrochloride of the methyl ester of cysteine the methyl ester of 2-(α-ethyl-γ-pyridyl)-Δ^2-thiazoline-4-carboxylic acid was synthesized.

4. By reacting the amide of γ-pyridylacetic acid with phosphorus oxychloride γ-(cyanomethyl)-pyridine was obtained.

5. By condensing β- and γ-(cyanomethyl)-pyridines with cysteamine β- and γ-pyridyl-2-thiazolinyl-Δ^2-methanes respectively were obtained.

6. By condensing β- and γ-(cyanomethyl)-pyridines with hydrogen sulfide the thiomides of β- and γ-pyridylacetic acids were synthesized.

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STUDIES IN THE FIELD OF 2-(β-AND γ-PYRIDYL)-Δ^2-THIAZOLINES

III. THE SYNTHESIS OF 2-PYRIDYLTHIAZOLINES, THEIR 4-CARBOXYLIC ACIDS, AND THEIR 2-METHYL SUBSTITUENTS

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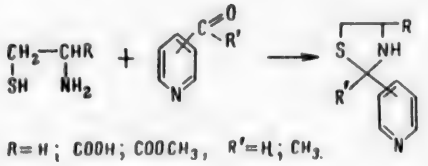
pp. 1483-1488, May, 1961
Original article submitted May 23, 1960

In preceding papers [1, 2] we described a series of 2-pyridyl substituted Δ^2-thiazolines which were of interest for the study of biological activity. In the present paper we describe closely related compounds which are derivatives of thiazoline and contain β- and γ-pyridine residues. These substances may be of interest because of their ability to be hydrolyzed under milk conditions with the formation of mercaptoamines and mercaptoamino acids [3]. For example, use is made in medicine of ethyl 2-(2'-thiazolidine-4'-carboxy)-phenylacetate (leucogen) [4], which has an antileucopenic action.

We carried out the formation of the thiazolidine ring in the usual way, by the action of a carbonyl compound with cysteine and its esters or with cysteamine [5].

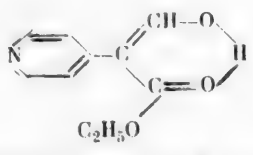


R=H; COOH; $COOCH_3$, R'=H; CH_3.

The reaction in the case of pyridyl aldehydes was exothermal and very rapid; it took place by stirring in 50% alcohol; in the case of β- and γ-pyridylmethyl ketone, reaction occurred at the temperature of a boiling alcohol solution and in the presence of sodium acetate.

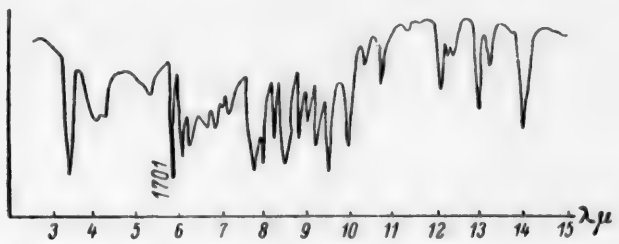
We tried to produce the pyridine analogs of leucogen by reaction of cysteine with ethyl formylpyridylacetates. These esters, of which the β-isomer was not described in the literature, were obtained by Claisen condensation of esters of β- and γ-pyridylacetic acids with ethyl formate [6]. However, we showed that these esters existed entirely in the hydroxymethylene form and under the conditions which we used did not condense with cysteine or its esters, and when heated with orthoformic ester and ethyl alcohol [7] or with an alcoholic solution of hydrogen chloride did not form acetals of formylpyridylacetic acid, but were split with formation of the corresponding pyridyl acetates.

Such behavior of the presumed formylpyridylacetates led us to conclude that they occurred completely in the hydroxymethylene form, that is, they were α-pyridyl-β-hydroxyacrylates.



This structure was confirmed by study of the infrared spectra of these compounds, which showed that the absorption band of carbonyl and hydroxyl groups were strongly shifted toward the short wave lengths (figure).

It should be observed that thiazolidine compounds, known to be very unstable substances, when substituted in position 2 by the pyridine residue undergo a further decrease in stability of the ring. They are hydrolyzed with opening of the thiazolidine ring under the influence of aqueous solutions of alkali or potash, but are stable with respect to ammonia and sodium bicarbonate. Hydrolysis occurs very easily in the presence of dilute acids at room temperature, and even the hydrochlorides in water solution are very quickly hydrolyzed with rupture of the thiazolidine ring. The substances are also partly decomposed by vacuum distillation. The imino group in the thiazolidine ring of these substances has the usual properties of a secondary amine. In the presence of sodium alcoholate it reacts with chloroacetonitrile. This strengthens the thiazolidine ring. In attempts to carry out the reaction of cyanethylation we obtained an oily substance which could not be purified.



Infrared spectrum of ethyl 3-pyridyl-β-hydroxyacrylate.

EXPERIMENTAL

2-(β-Pyridyl)-thiazolidine (I). A solution of 0.77 g of cysteamine and 1.29 g of β-pyridylaldehyde [8] in 10 ml of 50% alcohol was stirred for one hour at room temperature; after this the reaction for a free mercapto group (with sodium nitroprusside) disappeared. The solvent was removed in a vacuum and the oily residue was distilled; b.p. 141-142° (0.4 mm). We obtained 1.2 g (74.4%) of a colorless, oily substance, insoluble in water and petroleum ether, soluble in alcohol, ether, and other organic solvents.

Found %: N 17.10. $C_8H_{10}N_2S$. Calculated %: N 16.80.

Hydrochloride, from anhydrous alcohol. Colorless crystals. M.p. 172-174° (decomp.).

Found %: C 40.07; H 4.78; N 11.43; S 13.04; Cl' 29.62. $C_8H_{10}N_2S \cdot 2HCl$. Calculated %: C 40.17; H 5.05; N 11.71; S 13.40; Cl' 29.65.

Picrate, from alcohol; recrystallized from glacial acetic acid, light yellow prisms. M.p. 174-176° (decomp.).

Found %: N 17.75. $C_8H_{10}N_2S \cdot C_6H_3O_8N_3$. Calculated %: N 17.72.

2-(β-Pyridyl)-thiazolidine-4-carboxylic acid (II). A solution of 1.21 g of cysteine and 1.21 g of β-pyridine aldehyde in 50 ml of 50% alcohol was stirred at room temperature for 0.5 hours. Then the solvent was partly removed in a vacuum and the residue was cooled in a cooling mixture; colorless crystals separated. We obtained 1.77 g (84%) of a substance, soluble in water and alcohol, insoluble in organic solvents. Needles from anhydrous alcohol. M.p. 136-137°.

Found %: C 51.62; H 4.82; N 13.25; S 15.65. $C_9H_{10}O_2N_2S$. Calculated %: C 51.51; H 4.76. N 13.30; S 15.29.

Ethyl 2-(2'-thiazolidyl)-phenylacetate (III). To 11.52 g of ethyl formylphenylacetate we added 3.85 g of cysteamine. Heating occurred and then the cysteamine dissolved. The solution was shaken in a rocker for five hours; to the resulting oily reaction mass we added 30 ml of anhydrous alcohol and allowed it to stand overnight. The crystals which separated were soluble in alcohol, ether, acetone, and other organic solvents, insoluble in water. Yield 7.8 g (62%). Colorless needles from alcohol. M.p. 89-90°.

Found %: C 61.79; H 6.79; N 6.17; S 13.00. $C_{13}H_{17}O_3NS$. Calculated %: C 62.02; H 6.83; N 5.59; S 12.77.

Hydrochloride, from anhydrous alcohol, colorless crystals which hydrolyzed on standing in water solution. M.p. 162-164° (decomp.).

Found %: Cl 12.59. $C_{13}H_{17}O_2N \cdot HCl$. Calculated %: Cl 12.70.

Ethyl α-(3-pyridyl)-β-hydroxyacrylate (IV). To dry sodium ethylate obtained from 1.2 g of metallic sodium we added with energetic stirring a mixture of 5 g of ethyl β-pyridylacetate [9] and 25 ml of ethylformate. The reaction was exothermal. The reaction mass was gradually heated to 105° and heating at this temperature was continued for 25 hours; the reaction mass gradually became yellow. Then the reaction mass was transferred to ice water and the organic layer was separated. The water layer was acidified with acetic acid (5 ml) with cooling; after some time a yellow precipitate came down and was filtered off and washed with water. Yield 3.5 g (55%). Colorless prisms from acetone (with addition of charcoal). M.p. 124-125° (decomp.). The substance gave a violet color with ferric chloride and decolorized bromine water. It was insoluble in water, easily soluble in organic solvents.

Found %: C 62.12; H 5.60; N 7.24. $C_{10}H_{11}O_3N$. Calculated %: C 62.20; H 5.73; N 7.25.

When heated with an alcoholic solution of hydrogen chloride or orthoformic ester it was decomposed to ethyl β-pyridylacetate. Hydrochloride, prisms from alcohol.

Found %: C 53.71; H 5.85; N 7.01; Cl 17.80. $C_9H_{11}O_2N \cdot HCl$. Calculated %: C 53.52; H 5.99; N 6.94; Cl 17.60.

Ethyl α-(4-pyridyl)-β-hydroxyacrylate [6] was obtained like the β-homolog with a yield of 34% against the yield of 19% reported in the literature. With a solution of hydrogen chloride in alcohol or orthoformic ester, it was decomposed by boiling to give the γ-pyridylacetate which was isolated in the form of the hydrochloride. Colorless prisms. M.p. 164-165° (from alcohol).

Found %: C 53.34; H 6.25; N 6.92; Cl 17.72. $C_9H_{11}O_2N \cdot HCl$. Calculated %. C 53.52; H 5.99; N 6.94; Cl 17.60.

2-Methyl-2-(β-pyridyl)-thiazolidine (V). To a solution of 9 g of 3-pyridylmethyl ketone [10] in 15 ml of anhydrous methyl alcohol in a stream of nitrogen we added 3.85 g of cysteamine with stirring. The solution was boiled for two hours (to absence of the reaction with sodium nitroprusside for mercapto groups), then the alcohol was removed in a vacuum. The oily residue was distilled, b.p. 131-132° (0.6 mm). A colorless, oily substance, easily soluble in organic solvents, insoluble in water. Yield 6.8 g (76%).

Found %: N 15.46. $C_9H_{12}N_2S$. Calculated %: N 15.53.

Hydrochloride, colorless prisms. M.p. 170-172° (decomposition; from anhydrous alcohol).

Found %: C 42.63; H 5.27; N 11.19; S 12.32; Cl 28.19. $C_9H_{12}N_2S \cdot 2HCl$. Calculated %: C 42.57; H 5.58; N 11.08; S 12.66; Cl 28.00.

Picrate, yellow prisms. M.p. 128-129° (from alcohol).

Found %: C 44.19; H 3.63; N 16.98; S 8.18. $C_9H_{12}N_2S \cdot C_6H_3O_7N_3$. Calculated %: C 44.08; H 3.69; N 17.11; S 7.83.

2-Methyl-2-(γ-pyridyl)-thiazolidine (VI). We dissolved 3.85 g of cysteamine in 15 ml of anhydrous methyl alcohol which was saturated with nitrogen and contained 9 g of γ-pyridylmethyl ketone [6]. The solution was boiled with stirring for one hour. After this, crystals began to form in the reaction mixture. After cooling, we obtained 8.52 g (95%) of a substance easily soluble in alcohols, ether, and ethyl acetate, insoluble in water. Colorless platelets. M.p. 160-161° (from alcohol).

Found %: C 59.71; H 6.60; N 15.43; S 17.78. $C_9H_{12}N_2S$. Calculated %: C 59.95; H 6.70; N 15.33; S 17.77.

Methyl 2-methyl-2-(β-pyridyl)-thiazolidine-4-carboxylate (VII). To methyl cysteinate hydrochloride obtained from 6.04 g of cysteine [11] and dissolved in 50 ml of anhydrous methyl alcohol was added 9 g of β-pyridylmethyl ketone and 5 g of anhydrous sodium acetate in 75 ml of anhydrous methyl alcohol. The mixture was boiled in a stream of nitrogen with stirring for eight hours. After filtration of the sodium chloride, the alcohol was removed in a vacuum, and from the remaining yellow, oily substance which was soluble in alcohols, ether, and ethyl acetate, and insoluble in water, we obtained the picrate by action of a water solution of picric acid. Yellow crystals from acetone. M.p. 150-151°.

Found %: C 44.08; H 3.70; N 15.00; S 6.75. $C_{11}H_{12}O_2N_2S \cdot C_6H_3O_7N_3$. Calculated %: C 43.70; H 3.67; N 14.99; S 6.88.

Hydrochloride, colorless crystals. M.p. 163-165° (from alcohol).

Found %: Cl 22.54. $C_{11}H_{14}O_2N_2S \cdot 2HCl$. Calculated %: Cl 22.78.

Methyl 2-methyl-2-(γ-pyridyl)-thiazolidine-4-carboxylate (VIII). To a solution of methyl cysteinate hydrochloride (from 1.21 g of cysteine) in 10 ml of anhydrous methanol saturated with nitrogen was added 2 g of γ-pyridylmethyl ketone and 1 g of anhydrous sodium acetate, dissolved in 15 ml of anhydrous methanol. The reaction mixture was boiled for three hours in a stream of nitrogen with stirring. After filtration of the precipitated sodium chloride and partial removal of the solvent in a vacuum, crystals began to separate. Yield 1.87 g (79%). A colorless substance, insoluble in water, soluble in alcohols, ether, and ethyl acetate. M.p. 118-119° (from ethanol).

Found %: C 55.56; H 5.84; N 11.51; S 13.95. $C_{11}H_{14}O_2N_2S$. Calculated %: C 55.48; H 5.91; N 11.70; S 13.89.

2-(β-Pyridyl)-N-cyanomethylthiazolidine (IX). In a solution obtained from 0.14 g of metallic sodium in 20 ml of anhydrous alcohol was placed 1 g of (I) and 0.91 g of chloroacetonitrile. The reaction mixture was boiled with stirring for three hours. After cooling and filtration of the sodium chloride, the alcohol was removed in a vacuum and the oily residue was treated with several drops of water and the solution was extracted with ether. The ether extract was dried with magnesium sulfate and the solvent was removed in a vacuum. After some time, crystals separated from the oily residue and were washed with ether. We obtained 0.2 g (16.2%) of substance in the form of colorless needles. M.p. 110-111°.

Found %: C 58.21; H 5.26; N 20.52; S 15.91. $C_{10}H_{11}N_3S$. Calculated %: C 58.51; H 5.40; N 20.46; S 15.62.

SUMMARY

1. By condensation of β-pyridylaldehyde with cysteine and cysteamine we obtained 2-(β-pyridyl)-thiazolidine and 2-(β-pyridyl)-thiazolidinecarboxylic acid and its esters.

2. By condensation of β- and γ-pyridylmethyl ketones with methyl cysteinate and cysteamine we synthesized the corresponding esters of 2-methyl-(β- and γ-pyridyl)-thiazolidine-4-carboxylic acid and 2-methyl-(β- and γ-pyridyl)-thiazolidines.

3. By condensation of ethylformylphenylacetate with cysteamine we synthesized ethyl 2-(2'-thiazolidyl)-phenylacetate.

4. By condensation of ethyl β-pyridylcarboxylate with ethyl formate we obtained ethyl formyl-β-pyridylacetate and showed that it was the enol.

5. By condensation of 2-(β-pyridyl)-thiazolidine with chloroacetonitrile we obtained 2-(β-pyridyl)-N-cyanomethylthiazolidine.

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STUDIED IN THE FIELD OF 2-(β- AND γ-PYRIDYL)-Δ^2-THIAZOLINES.

V. SYNTHESIS OF ESTERS OF 2-THIAZOLYL-Δ^2-PHENYL- AND PYRIDYLACETIC ACIDS

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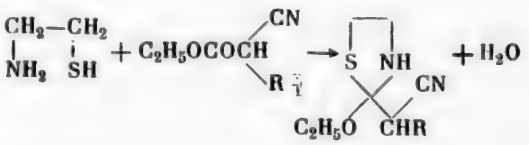
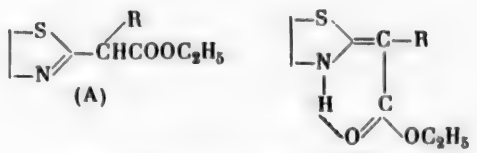
Original article submitted May 23, 1960

In carrying out our earlier experiments we synthesized Δ^2-thiazolines substituted in the second position by the pyridine ring directly [1, 2], and Δ^2-thiazolines in the second position of which the pyridine ring was joined through a methylene group [2]. It was interesting to obtain the analogous compounds with pyridine joined to the thiazoline ring by a methylene group which was substituted with an ester residue. We would expect that such a substance could have a definite pharmacological action, considering the known activity of 2-benzyl-Δ^2-thiazoline [3] and the activity of a whole series of substances with ester groups in the methylene group which joins two cyclic residues, for example, spasmolytin (diethylaminoethyl diphenylacetate hydrochloride), or ritalin, methyl phenyl-2-piperidyl acetate.

We chose the following path for the synthesis of this type of compound: in the reaction of cysteamine with ethyl (β- or γ-pyridyl)-cyanoacetate we would expect cyclization of the thiazoline ring with evolution of ammonia, but at the same time the possibility would exist of reaction of both components between the ester group and the active group $-SH$ or $-NH_2$ with formation of a thiazolidine ring. Such a condensation has been described [4, 5] in the reaction of ethylene imine and hydrogen sulfide (the components which give cysteamine) with ethyl acetate with formation of a thiazolidine derivative in 70% yield. In our case, the following course of the reaction would be possible.



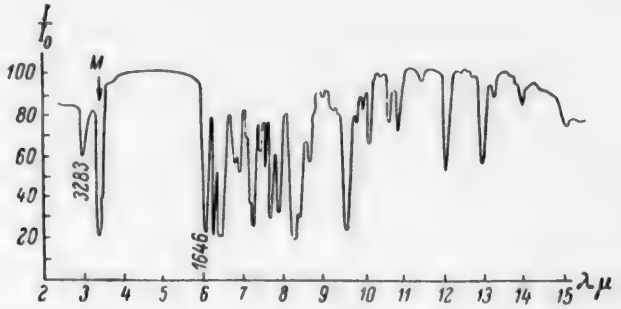
However, the nitrile group is more active than the ester group toward cysteamine. The reaction went with evolution of ammonia and it could be expected that the resulting compound would be the thiazoline derivative (A). The basicity of this compound was considerable weakened; the nitrogen of the thiazoline ring did not form salts even with mineral acids. The strength of the ring (with respect to acid hydrolysis) also fell sharply; for example, the hydrochloride of the diethylaminoethyl ester of phenyl-(2-thiazolidin-Δ^2)-acetic acid was hydrolyzed very rapidly in water solution at room temperature with rupture of the ring at the S–C bond.



(A) (B)

R = phenyl, β- and γ-pyridyl

Saponification of the ester group was difficult; a solution of barium hydroxide did not saponify it with boiling (evidently because of the insolubility of the substance in it), and alcoholic alkali split the ring with addition of a molecule of water at the S–C bond with simultaneous decarboxylation. The properties of the resulting expected substituted 2-thiazolinyl-Δ^2-phenyl- and pyridylacetic acids could be explained by the fact that these compounds evidently did not have the structure of derivatives of Δ^2-thiazoline, but were derivatives of thiazolidine with an exocyclic double bond, formed by prototropic rearrangement of the hydrogen from the α-carbon to the nitrogen of the thiazoline ring (B). These structures were confirmed by the presence in the infrared spectra of these compounds of absorption bands corresponding to the NH group (3283 cm^{-1}) and a strong shift of carbonyl (1646 cm^{-1}) (Figure).



Infrared spectrum of the ethyl ester of γ-pyridyl-(2-thiazolinyl-Δ^2)-acetic acid.

Since the ethyl esters of β- and γ-pyridylcyanoacetic acids have not been described in the literature, the formation of the thiazoline ring was first carried out on the basis of the ethyl ester of phenylacetic acid with a yield of 77%.

Preparation of the starting ethyl esters of β- and γ-pyridylcyanoacetic acids was carried out by the Claisen synthesis from β- and γ-cyanomethylpyridines [2] and diethyl carbonate in the presence of sodium alcoholate. The γ-homolog reacted very sluggishly with cysteamine, and cysteamine is oxidized by prolonged boiling in alcohol. As a result of the reaction we isolated the expected thiazoline derivative with a yield of about 15%, and found a considerable amount of unreacted starting ester.

EXPERIMENTAL

Ethyl ester of 2-thiazolinyl-Δ^2-phenylacetic acid (I). A solution of 22.7 g of ethyl phenylacetate and 7.7 g of cysteamine in 40 ml of anhydrous alcohol was boiled in a stream of nitrogen with stirring for eight hours; then the copious evolution of ammonia gradually stopped and the reaction for the mercapto group (with sodium nitroprusside) disappeared. After standing over night, colorless crystals came down and were washed with alcohol and acetone. We obtained 19.2 g (77%) of a substance insoluble in water, easily soluble in alcohol, acetone, ether, and ethyl acetate. Colorless prisms from alcohol. M.p. 60-61°.

Found %: C 62.30; H 6.21; N 5.82; S 13.04. $C_{13}H_{15}O_2NS$. Calculated %: C 62.55; H 6.07; N 5.62; S 12.90.

N-(Phenylacetyl)-cysteamine (II). We boiled 2.49 g of (I) with stirring in 25 ml of 0.4 N barium hydroxide solution for three hours. The precipitate which was filtered off gave no melting point depression with the original (I). It was dissolved in alcohol and treated with an alcohol solution of potassium hydroxide (0.4 N KOH). The solution was heated to boiling. After removal of the solvent in a vacuum the dry residue was extracted with ether. The ether was removed and the resulting crystalline substance was recrystallized from alcohol; colorless crystals, m.p. 54-55°, insoluble in water, easily soluble in organic solvents. The substance gave a reaction for the free mercapto group (with sodium nitroprusside). Yield quantitative.

Found %: C 61.61; H 6.69; N 7.21; S 16.13. $C_{10}H_{13}ONS$. Calculated %: C 61.52; H 6.71; N 7.17; S 16.42.

Diethylaminoethyl ester of 2-thiazolinyl-Δ^2-phenylacetic acid (III). In an apparatus for vacuum distillation, fitted with a fractionating column, we placed a solution of 4.98 g of (I) in 10 ml of dry, freshly distilled diethylaminoethanol and added to it sodium diethylaminoethanolate (obtained from 0.1 g of metallic sodium in 5 ml of

diethylaminoethanol). The reaction mixture was heated at a bath temperature of 90-95° (80-30 mm) for four hours, reaching a final vacuum of 15 mm. After careful removal of excess diethylaminoethanol the resulting oily substance was treated with concentrated hydrochloric acid with cooling. The hydrochloride which formed was neutralized with sodium bicarbonate and the substance was extracted with ether; the extract was washed with water, dried with magnesium sulfate with the addition of charcoal, and then the solvent was removed in a vacuum. We obtained 5.3 g (82%) of oily substance (III), insoluble in water, soluble in organic solvents. The substance formed salts. a) When the base dissolved in ether was saturated with dry hydrogen chloride it gave a very hygroscopic hydrochloride which was hydrolyzed in water solution at room temperature with rupture of the thiazoline ring at the S–C bond: the reaction for the mercapto group with sodium nitroprusside appeared; the solution became cloudy. b) The action of a saturated solution of salicylic acid in alcohol on (III), after standing at room temperature and then cooling, gave the salicylate in quantitative yield. Colorless prisms from alcohol with m.p. 131-132°, very difficultly soluble in boiling water, easily soluble in alcohols and other organic solvents.

Found %: C 62.63; H 6.40; N 6.03; S 7.22. $C_{17}H_{24}O_2N_2S \cdot C_7H_6O_3$. Calculated %: C 62.85; H 6.51; N 6.12; S 7.01.

Diethylaminoethyl ester of 2-thiazolinyl-Δ^2-phenylacetic acid methiodine (IV). To a solution of 2.5 g of (III) in 10 ml of anhydrous benzene was added 6 g of methyl iodide and after stirring the mixture it was left over night at room temperature. The crystals which precipitated were washed with benzene. The yield was quantitative. Colorless needles from anhydrous alcohol; m.p. 163-164°, difficultly soluble in water, easily so in alcohols.

Found %: C 46.86; H 5.82; N 5.78; S 6.76; I 27.00. $C_{18}H_{27}O_2N_2SI$. Calculated %: C 46.88; H 5.89; N 6.07; S 6.95; I 27.40.

Ethyl ester of β-pyridylcyanoacetic acid (V). In a solution of sodium ethylate obtained from 1.2 g of metallic sodium in 20 ml of anhydrous alcohol we added with stirring 5.9 g of β-cyanomethylpyridine [2] and 30 ml of diethyl carbonate. The mixture was boiled at 90-100° for four hours, then cooled and poured into 30 ml of water and the salt separated. The water layer was acidified with glacial acetic acid (4 ml) and ether was added to it; with shaking, orange crystals formed at the border of the water and ether layers. Yield 7.6 g (80%). Yellow prisms from acetonitrile or ethyl acetate, well soluble in alcohols, acetone and ethyl acetate, poorly so in ether. M.p. 103-104°.

Found %: C 62.99; H 5.38; N 14.61. $C_{10}H_{10}O_2N_2$. Calculated %: C 63.12; H 5.30; N 14.72.

Ethyl ester of 2-thiazolinyl-Δ^2-β-pyridylacetic acid (VI). A solution of 0.77 g of cysteamine and 1.9 g of (V) in 10 ml of anhydrous alcohol was boiled under conditions analogous to those of (I). After removal of the solvent in a vacuum we obtained an oily substance soluble in organic solvents, insoluble in water. From it, by the action of an alcoholic solution of hydrogen chloride, we isolated 2.2 g (79%) of a crystalline monohydrochloride. Colorless prisms from alcohol (with addition of charcoal), easily soluble in water and alcohols, insoluble in chloroform and other organic solvents. M.p. 166-167° (decomp.).

Found %: C 50.61; H 5.27; N 9.52; S 11.11; Cl 12.36. $C_{12}H_{14}O_2N_2S \cdot HCl$. Calculated %: C 50.25; H 5.27; N 9.75; S 11.20; Cl 12.35.

Ethyl ester of γ-pyridylcyanoacetic acid (VII). To anhydrous sodium ethylate prepared from 1.2 g of metallic sodium in 30 ml of anhydrous alcohol we added with stirring a solution of 5.9 g of γ-cyanomethylpyridine [2], in 30 ml of diethyl carbonate. The mixture was heated at 100° for four hours; then we added dropwise 20 ml of dry toluene and distilled off the alcohol. The reaction mass after cooling was dissolved in 30 ml of water. The organic layer was separated and the water was acidified with glacial acetic acid; we isolated yellow crystals in quantitative yield. Colorless prisms from ethanol (with addition of charcoal), m.p. 210-212°, insoluble in ether, benzene, and chloroform, very difficultly soluble in ethyl acetate, easily soluble in alcohols. When boiled with a 10% solution of alkali, ammonia was evolved. The substance was also obtained under conditions analogous to those of (V) with 64% yield.

Found %: C 63.00; H 5.14; N 14.84. $C_{10}H_{10}O_2N_2$. Calculated %: C 63.12; H 5.29; N 14.72.

Ethyl ester of 2-thiazolinyl-Δ^2-γ-pyridylacetic acid (VIII). We added 3.85 g of cysteamine to 9.5 g of (VII) dissolved in 120 ml of anhydrous alcohol in a stream of nitrogen with stirring. The reaction mixture was boiled for 30 hours; ammonia was evolved. After disappearance of the reaction for mercapto groups (with sodium nitroprusside) the reaction mixture was cooled; crystals separated (7.7 g, 81%) which gave no melting point depression with the

starting (VII). The mother liquor was evaporated in a vacuum. After standing for two days the oily residue partly crystallized. The crystals were filtered off, washed with alcohol and with ether. Colorless prisms from anhydrous alcohol, m.p. 100-101°, easily soluble in alcohols, ether, and other organic solvents, insoluble in water. Yield 1.8 g (15%).

Found %: C 57.46; H 5.73; N 11.08; S 12.73. $C_{12}H_{14}O_2N_2S$. Calculated %: C 57.51; H 5.64; N 11.20; S 12.81.

SUMMARY

1. We have condensed β- and γ-(cyanomethyl)-pyridines with diethyl carbonate and synthesized ethyl esters of (β- and γ-pyridyl)-cyanoacetic acid.

2. We have condensed the ethyl esters of (β- and γ-pyridyl)-cyanoacetic acid and the ethyl ester of phenyl-cyanoacetic acid with cysteamine and synthesized the ethyl esters of (2-thiazolinyl-Δ^2)-β- and γ-pyridylacetic and (2-thiazolinyl-Δ^2)-phenylacetic acids respectively.

3. By transesterification of the ethyl ester of (2-thiazolinyl-Δ^2)-phenylacetic acid with diethylaminoethanol we have synthesized the diethylaminoethanol ester of (2-thiazolinyl-Δ^2)-phenylacetic acid and obtained its methiodide.

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STUDIES IN THE PHENOXAZINE SERIES

III. GLYCINYL DERIVATIVES OF PHENOXAZINE

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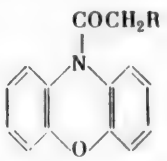
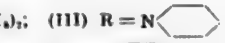
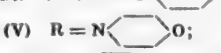
In a previous communication [1] we described the preparation of 10 substituted phenoxazines, including 10-(3-dimethylaminopropyl)-phenoxazine, the analog of the highly active phenothiazine preparation, promazine. Considering that the introduction into the 10 position of phenothiazine of dialkylaminoacyl groups also produces pharmacologically active substances, for example, the hydrochloride of 10-(2-diethylaminoacetyl)-phenothiazine, diphazine [2], we carried out the synthesis of analogous phenoxazine derivatives. We also synthesized a series of derivatives of 1-aminophenoxazines, whose hydrochlorides, as is known, inhibit the development of tuberculosis bacteria in dilutions of $1 : 10^9$ [3]. There is also evidence that 2-(N,N-diethylglycylamino)-3-phenoxazone has tuberculostatic activity almost as great as streptomycin [4].

The starting substance for preparing 10-dialkylaminoacetylphenoxazines is phenoxazine which we obtained by heating o-aminophenol in the presence of iodine [5] and purified on a column with aluminum oxide [6]. Chloroacetylation of phenoxazine took place with good yield; it should be noted that 10-chloroacetylphenoxazine (I) has a strong irritating action on the skin and mucous membrane. Condensation of (I) with diethylamine, piperidine, N-methylpiperazine, and morpholine was carried out in boiling methylethyl ketone and gave oily reaction products (II-V) which gradually solidified when washed with water. The substances were purified by crystallization or distillation in a vacuum. Some of them were isolated as the hydrochlorides (II, IV).

The condensation of (I) with piperazine gave along with the 10-piperazinoacetylphenoxazine (VI) a product of condensation of two molecules of (I) with one molecule of piperazine (VII). The substances isolated after the reaction were separated mechanically in the form of crystals. All the compounds with substituents in the 10 position of the phenoxazine radical are well crystallized, stable substances with sharp melting points.



(I) R = Cl; (II) R = $N(C_2H_5)_2$; (III) R =  ;
(IV) R =  ; (V) R = ;
(VI) R = ; (VII) R =

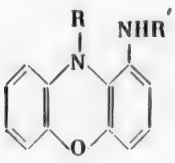
The starting substance for the derivatives of 1-aminophenoxazine was 1-nitrophenoxazine, synthesized from 2,6-dinitrochlorobenzene and o-aminophenol [7] with further closure of the resulting 2,6-dinitro-2'-hydroxydiphenylamine. Reduction [8] of 1-nitrophenoxazine with stannous chloride gave 1-aminophenoxazine hydrochloride with a yield of about 80%. 1-Aminophenoxazine hydrochloride (VIII) was poorly soluble in water, and attempts to obtain a more soluble salt were not successful. The formaldehydebisulfite derivative of 1-aminophenoxazine (IX) was also not very soluble. In distinction from the results of Kehrmann who in the acetylation of hydrochloride (VIII) with acetyl chloride obtained 1-acetylaminophenoxazine with m.p. 197°, we obtained in this reaction two substances: 1-acetylaminophenoxazine (X) with m.p. 213-215° whose alcohol solution with addition of a water solution of ferric

TABLE 1*

Substance No.	Activity in vitro in raising						
	Micobaclerium tuberculesis				pathogenic fungi		
	academy strain		H37Rv strain				
	without serum	with serum	without serum	with serum	micro-sporum	tricho-phyton	achorion
(VIII)	1 : 32000	1 : 64000	—	1 : 100000	1 : 16000	1 : 8000	1 : 4000
(IX)	1 : 128000	1 : 16000	1 : 4000	1 : 2000	—	—	1 : 1000
(X)	—	1 : 8000	—	1 : 6000	1 : 4000	1 : 4000	1 : 4000
(XI)	1 : 16000	1 : 4000	—	1 : 16000	—	—	—
(XII)	1 : 32000	1 : 1000	1 : 64000	1 : 4000	1 : 1000	1 : 1000	1 : 2000
(XIV)	1 : 64000	1 : 16000	1 : 512000	1 : 128000	1 : 4000	1 : 2000	1 : 4000
(XV)	—	—	—	—	1 : 30000	1 : 16000	1 : 30000
(XVI)	—	—	—	—	1 : 1000	1 : 1000	1 : 2000
(XVII)	1 : 16000	1 : 64000	1 : 16000	1 : 8000	—	—	—
(III)	—	—	—	—	1 : 2000	1 : 2000	1 : 2000

* All the compounds were studied by O. O. Makeeva and S. N. Milovanova in the Division of Chemotherapy of the VNIKhFI under the direction of G. N. Pereshin with respect to their action on various microorganisms (a spectrum of 16 forms).

chloride became dark red, oxidizing to phenoxazone, and 1-acetylamino-10-acetylphenoxazine (XI) with m.p. 168° which was not changed by addition of ferric chloride since there is no possibility of such an oxidation in it. The monoacetyl derivative (X) on further acetylation is converted into the diacetyl derivative (XI).



(VIII) R = R′ = H; (IX) R = H; R′ = CH_2SO_3Na; (X) R = H; R′ = $COCH_3$; (XI) R = R′ = $COCH_3$; (XII) R = R′ = $COCH_2Cl$; (XIII) R = H; R′ = $COCH_2Cl$; (XIV) R = H; R′ = $COCH_2N(C_2H_5)_2$; (XV) R = H; R′ = $COCH_2N$⟨⟩; (XVI) R = R′ = $COCH_2N(C_2H_5)_2$; (XVII) R = R′ = $COCH_2N$⟨⟩; (XVIII) R = R′ = $COCH_2O$⟨⟩O; (XIX) R = H; R′ = $SO_2C_6H_4NHCOOCH_3$-n.

Acetylation of the dimethylaminoacetyl chloride even under very mild conditions leads to complete tarring of the reaction mass; therefore, we first prepared 1-chloroacetylaminophenoxazine which was then condensed with a secondary aliphatic or cyclic amine. With excess chloroacetyl chloride (2.5 mole per 1 mole of 1-aminophenoxazine) we obtained a good yield of 1-chloroacetylamino-10-chloroacetylphenoxazine (XII); the reaction of 1 mole of 1-aminophenoxazine and 1 mole of chloroacetyl chloride gave a mixture of two substances; one of them, obtained with a yield of about 30% was 1-chloroacetylaminophenoxazine (XIII); the other substance, considerably more difficultly soluble, did not contain chloride and we did not succeed in obtaining it completely pure. It was apparently the product of the condensation of 1 molecule of chloroacetyl chloride with 2 molecules of 1-aminophenoxazine. The condensation of (XIII) with diethylamine and piperidine was carried out in boiling methylethyl ketone.

The bases 1-diethylamino- (XIV) and 1-piperidinoacetylaminophenoxazine (XV) were very dark, oily substances; the hydrochlorides were light gray crystalline substances which quickly darkened in air, and even after repeated recrystallizations did not have sharp melting points.

Condensation of (XII) with diethylamine, piperidine, and morpholine gave the corresponding derivatives (XVI, XVII, and XVIII). Their hydrochlorides were colorless substances which crystallized with one molecule of water. Condensation of (I) with N-carbomethoxysulfanyl chloride gave 1-(carbomethoxysulfanilamido)-phenoxazine (XIX) and saponification of the methoxyl group gave a tarry substance which could not be purified.

Compounds with free 10 position in the ring crystallize badly and darken rapidly on standing; they do not have sharp melting points. In Table 1 we give the bacteriostatic activity of a number of preparations toward tuberculosis bacteria and pathogenic fungi. The remaining preparations were not active toward these microbes.

TABLE 2

Compound No.	Solvent	M. p.	Formula	Found, %				Calculated, %			
				C	H	N	Cl	C	H	N	Cl
(XIV)	Alcohol	—*	$C_{18}H_{21}O_2N_3 \cdot HCl \cdot H_2O$	—	—	11.77	9.66	—	—	11.50	9.73
(XV)		—*	$C_{19}H_{21}O_2N_3 \cdot HCl$	—	—	12.21	—	—	—	11.70	—
(XVI)		235—236°	$C_{24}H_{32}O_3N_4 \cdot HCl$	62.60	6.36	11.73	—	62.40	7.2	12.13	—
(XVII)	Dilute alcohol	238—241	$C_{26}H_{32}O_3N_4 \cdot 2HCl \cdot H_2O$	57.82	6.67	—	—	57.80	6.7	—	—
(XVIII)		236.5—237 *	$C_{24}H_{28}O_5N_4 \cdot 2HCl \cdot H_2O$	52.95	6.11	—	—	53.00	5.90	—	—
(II)	Ethyl acetate	—	$C_{18}H_{20}O_2N_2 \cdot HCl \cdot H_2O$	—	—	10.00	8.08	—	—	10.21	8.01
(V)	Ethyl acetate + ether	90—91	$C_{18}H_{18}O_3N_2$	69.11	5.82	—	—	69.68	5.85	—	—
(VI)	Alcohol	154—155	$C_{18}H_{19}O_2N_3$	69.69	6.24	13.60	—	69.84	6.19	13.58	—
(VII)	Dioxane	230—231	$C_{32}H_{28}O_4N_4$	—	—	10.36	—	—	—	10.58	—
(III)	Alcohol	110—112	$C_{19}H_{20}O_2N_2$	73.17	6.61	—	—	73.98	6.69	—	—
(IV)		115—116	$C_{19}H_{21}O_2N_3$			13.03				12.99	

* On heating in a capillary it gradually darkened and decomposed.

EXPERIMENTAL

Phenoxazine. A mixture of 109 g of o-aminophenol and 1 g of crystalline iodine was heated to 270° during 1.5-2 hours and kept at 270-280° for 4 hours. The water which formed gradually distilled off. The contents of the flask were poured hot onto a slab: after cooling, the dark, brittle mass was ground in a mortar and treated with boiling benzene (6-7 times with 750 ml in two hours). The benzene solution was heated with charcoal, filtered, and purified by passage through a column with aluminum oxide (diameter 30 mm, height 500 mm, 4 columns). Washing of the residue of phenoxazine was carried out with benzene. After distillation of the benzene in a vacuum almost to dryness, the light gray crystalline precipitate was filtered off, washed with a small amount of cold benzene, and dried. Yield of phenoxazine 28-30 g (30-33%); m.p. 153-155°.

10-Chloroacetylphenoxazine (I). A mixture of 12 g of phenoxazine, 50 ml of dry benzene, and 10 ml of chloroacetyl chloride was boiled for one hour. After cooling, the precipitate which came down was filtered off and recrystallized from alcohol. We obtained 14 g of a colorless, crystalline substance (82.5%), m.p. 145-146.5°; soluble in acetone, methylethyl ketone, and alcohol.

Found %: C 65.01; H 3.90; N 5.68; Cl 13.37. $C_{14}H_{10}O_2NCl$. Calculated %: C 64.90; H 3.86; N 5.4; Cl 13.70.

1-Aminophenoxazine (VIII). To a hot, filtered solution of 8 g of the hydrochloride (VIII) in 2 liters of water was added 40 ml of a saturated solution of soda. The crystals which precipitated after cooling were filtered, washed with cold water, and dried in a vacuum desiccator. We obtained 6.1 g of a dark gray substance with m.p. 123-124°. After two recrystallizations from alcohol the m.p. of the fine, light gray crystals was 129-130°; they darkened in air and were soluble in hot water and organic solvents.

Found %: C 72.57; H 5.29. $C_{12}H_{10}ON_2$. Calculated %: C 72.71; H 5.09.

1-Aminophenoxazine-methylenesulfonic acid, sodium salt (IX). To a solution of 2 g of (VIII) in 10 ml of alcohol was added a solution of 1.5 g of formaldehyde-sodium bisulfite and then 1 ml of 40% sodium bisulfite solution. After boiling for half an hour, the precipitate which came down was filtered off and recrystallized from water with the addition of several drops of 40% sodium sulfite solution. The slightly colored substance crystallized with one molecule of water, and on the loss of this, it quickly darkened.

Found %: C 46.62; H 4.01. $C_{13}H_{11}O_4N_2SNa \cdot H_2O$. Calculated %: C 46.98; H 3.85.

1-Acetylaminophenoxazine (X). A mixture of 1 g of hydrochloride (VIII), 1 g of fused sodium acetate, 5 ml of acetic anhydride, and a small amount of zinc dust was boiled for five minutes. The solution was filtered hot and after cooling was poured into cold water; the oil which precipitated gradually crystallized. The substance was recrystallized from alcohol. We obtained 0.35 g of (X) with m.p. 213-215°. On standing in air, the substance became violet.

Found %: C 69.71; H 5.09; N 11.22. $C_{14}H_{12}O_2N_2$. Calculated %: C 69.97; H 5.04; N 11.66.

1-Acetylamino-10-acetylphenoxazine (XI) was obtained by carrying out the reaction as in the previous experiment, but with boiling for one hour. Colorless crystals (from alcohol) with m.p. 169-170°.

Found %: C 68.17; H 5.15; N 9.99. $C_{16}H_{14}O_3N_2$. Calculated %: C 68.08; H 5.00; N 9.93.

Substance (XI) gave no melting point depression with a sample obtained by acetylation of (X).

A mixture of 4.5 g of (X) and 5 ml of acetic anhydride was boiled for 30 minutes. The clear solution was poured into water, the precipitate was filtered off, and recrystallized from water, m.p. 168-170°.

1-Chloroacetylaminophenoxazine (XIII). To a suspension of 16.4 g of (VIII) in 160 ml of dry toluene with stirring we added at 3-4° a solution of 6.4 ml of chloroacetyl chloride in 64 ml of anhydrous toluene. After keeping for 10 minutes at this temperature we added 250 ml of ligroin and the mixture was left for a day in a refrigerator. The dark violet precipitate was filtered off, washed with ligroin, and dried. We obtained 20 g from which by boiling with water we extracted a light rose colored crystalline substance in the amount of 6.4 g with m.p. 310-313°. The substance contained chlorine and on standing in air or by recrystallization, darkened strongly.

1-Chloroacetylamino-10-chloroacetylphenoxazine (XII). A mixture of 10 g of (VIII), 100 ml of dry benzene, and 11 ml of chloroacetyl chloride was boiled for two hours, the benzene was distilled off in a vacuum, and the residue was twice recrystallized from glacial acetic acid. We obtained 10 g (56.5%) of (XII) with m.p. 179-181°. Colorless crystals, soluble in hot alcohol and acetone, insoluble in water.

Found %: C 55.03; H 3.53; Cl 20.13. $C_{16}H_{12}O_3N_2Cl_2$. Calculated %: C 54.73; H 3.44; Cl 20.20.

1-(4-Carbomethoxysulfanilamido)-phenoxazine (XIX). To a mixture of 2 g of hydrochloride (VIII) heated to 70° in 20 ml of a saturated solution of sodium chloride was added in the course of 5 minutes 2.35 g of N-carbomethoxysulfanyl chloride. The mixture was kept on a boiling water bath for two hours. After cooling, the precipitate was filtered off, washed with water, dried, and recrystallized from glacial acetic acid. M.p. 260-261°; colorless crystals.

Found %: C 57.82; H 4.28; N 10.00. $C_{20}H_{17}O_5N_3S$. Calculated %: C 58.39; H 4.17; N 10.21.

Condensation of (I), (XII), and (XIII) with diethylamine, piperidine, morpholine, methylpiperazine, and piperazine. A mixture of 1 mole of (I) or (XIII), 2.2 moles of diethylamine, or piperidine, morpholine, piperazine or methylpiperazine respectively and five times the weight of methylethyl ketone was boiled for 30 minutes. After cooling, the precipitate which came down, the hydrochloride of the secondary amine, was filtered off, and the filtrate was poured into water. The oil which separated was well washed with water dissolved in ethyl acetate, dried with ignited magnesium sulfate, and by addition of an alcoholic solution of hydrochloric acid, (II) (XIV-XVIII) were precipitated as hydrochlorides. In compounds (III-VII) the oil which separated after pouring into water crystallized and the substance was characterized as the base. In the reaction of (XII) we used 4.5 moles of amine (Table 2).

SUMMARY

1. Acylation of 1-aminophenoxazine with acetic anhydride and chloroacetyl chloride led to formation of two types of compounds: 1-acylaminophenoxazines and 1-acylamino-10-acylphenoxazines.

2. From 1-aminophenoxazine we obtained the Na salt of 1-aminophenoxazine-methylenesulfonic acid and 1-(4-carbomethoxysulfanilamido)-phenoxazine.

3. We carried out replacement of chlorine in 1-chloroacetylaminophenoxazine and 1-chloroacetylamino-10-chloroacetylphenoxazine by radicals of diethylamine, piperidine, and morpholine.

4. From phenoxazine we obtained 10-chloroacetylaminophenoxazine in which we replaced the chlorine by radicals of diethylamine, piperidine, methylpiperazine, and morpholine.

5. From the reaction of 10-chloroacetylaminophenoxazine with piperazine we obtained mono and disubstituted derivatives of piperazine.

6. A number of these preparations had tuberculostatic and antifungus activity.

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STUDIES IN THE PHENOXAZINE SERIES

IV. ACYL DERIVATIVES OF PHENOXAZINE AND 1-CARBETHOXY-3-AMINOPHENOXAZINE

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In continuation of our studies in the field of phenoxazine derivatives [1-3] we have synthesized some acyl derivatives of 1-carbethoxy-3-aminophenoxazine and unsubstituted phenoxazine, and also the amide of 3-nitrophenoxazine-1-carboxylic acid. 1-Carbethoxy-3-aminophenoxazine (I) was obtained from 3-nitrophenoxazine-1-carboxylic acid [4] through the acid chloride, ethyl ester, and reduction in the latter of the nitro group, with stannous chloride [2].

By boiling compound (I) with excess acetic anhydride we obtained two substances: 1-carbethoxy-3-ethylaminophenoxazine (II) and 1-carbethoxy-3-acetylamino-10-acetylphenoxazine (III). With longer boiling we obtained more of compound (III). In this substance the acetyl group in position 10 was easily saponified by heating with alcoholic alkali; at the same time the ester group was saponified and we obtained 3-acetylaminophenoxazine-1-carboxylic acid (IV).

The action on compound (I) of chloroacetyl chloride in benzene solution leads to the formation of the monoacetyl derivative only, 1-carbethoxy-3-(chloroacetylamino)-phenoxazine (V). It is interesting to note that under these conditions the chloroacetylation of 1-aminophenoxazine leads to the diacetyl compound, 1-chloroacetylamino-10-chloroacetylphenoxazine [3].

In the condensation of the chloroacetyl derivative (V) with diethylamine, piperidine, and morpholine, we obtained the corresponding 1-carbethoxy-3-(diethylaminoacetylamino)-phenoxazine (VI), 1-carbethoxy-3-(piperidinoacetylamino)-phenoxazine (VII), and 1-carbethoxy-3-(morpholinoacetylamino)-phenoxazine (VIII).

Condensation was carried out by heating (V) with an excess of the corresponding amine in methylethyl ketone, after which the reaction mass was poured into water. The condensation products were isolated as the bases which were crystalline substances easily soluble in all organic solvents. Their hydrochlorides were not stable and hydrolyzed when dissolved in water.

From the acid chloride of 3-nitrophenoxazine-1-carboxylic acid (IX) by the action of ammonia, diethylamine, and piperidine we obtained the corresponding substituted amides (X, XI, XII). In attempts to reduce the nitro group in these compounds we did not succeed in obtaining the corresponding amines, since the substances formed were not very stable and when isolated and purified they were converted to black, insoluble tars.

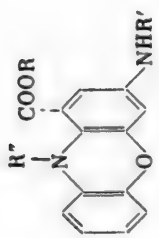
As is known [5] when phenoxazine is acylated with acetyl chloride by the Friedel-Crafts reaction, two monoacetyl derivatives are obtained, 10- and 3-acetylphenoxazine. We used this method for acetylation of phenoxazine with chloroacetyl chloride and isolated only the diacyl derivative: 3-chloroacetyl-10-chloroacetylphenoxazine (XIII) with a yield of 33%. The reaction was accompanied by much tarring. When the same reaction was carried out with 10-acetylphenoxazine we obtained 3-chloroacetyl-10-acetylphenoxazine (XIV) with a yield of 82%.

EXPERIMENTAL

1-Carbethoxy-3-acetylaminophenoxazine (II) and 1-carbethoxy-3-acetylamino-10-acetylphenoxazine (III). A mixture of 10 g of (I) and 50 ml of acetic anhydride was boiled for 20 minutes. The precipitate which separated on cooling was recrystallized from alcohol. Yield of (II) 3.5 g, yellow crystals with m.p. 222°.

Found %: N 9.33. $C_{17}H_{16}O_4N_2$. Calculated %: N 8.97.

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)
R	C_2H_5	C_2H_5	C_2H_5	H	C_2H_5	C_2H_5	C_2H_5	C_2H_5
R′	H	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_2Cl$	$COCH_2N(C_2H_5)_2$	$COCH_2N$	$COCH_2N$
R″	H	H	$COCH_3$	H	H	H	H	H



The mother liquor of acetic anhydride was treated with water. The resulting yellow crystalline precipitate of (III) was recrystallized from alcohol. Yield 6.7 g, m.p. 131-133°.

Found %: N 7.97. $C_{19}H_{18}O_5N_2$. Calculated %: N 7.90.

1-Carbethoxy-3-(chloroacetylamino)-phenoxazine (V). To a solution of 8 g of (I) in 150 ml of dry benzene was added a solution of 4.4 ml of chloroacetyl chloride in 15 ml of dry benzene; a bright green precipitate formed. The reaction mixture was heated with stirring for one hour. On cooling, we obtained 8.6 g; yellow crystals from a large amount of methanol with m.p. 218°.

Found %: C 58.61; H 4.54; N 8.46; Cl 10.96. $C_{17}H_{15}O_4N_2Cl$. Calculated %: C 58.87; H 4.33; N 8.08; Cl 10.24.

1-Carbethoxy-3-(diethylaminoacetylamino)-phenoxazine (VI). To a solution of 2 g of (V) in 30 ml of methylethyl ketone we added a solution of 1 g of diethylamine in 5 ml of methylethyl ketone; after 10 minutes heating to boiling, a precipitate formed consisting of diethylamine hydrochloride. Boiling was continued for 10 minutes more, and after cooling, the reaction mass was poured into water. The oil which precipitated quickly crystallized. Yield 3.1 g; yellow platelets with m.p. 100-104°. After recrystallization from a mixture of benzene and ligroin they had m.p. 105-107°.

Found %: C 65.04; H 6.27; N 10.78. $C_{21}H_{25}O_4N_3$. Calculated %: C 65.78; H 6.53; N 10.96.

1-Carbethoxy-3-(piperidinoacetylamino)-phenoxazine (VII) was obtained as described in the previous experiment. Yellow platelets from a mixture of benzene and ligroin, m.p. 144-145°.

Found %: C 67.32; H 6.29; N 10.41. $C_{22}H_{25}O_4N_3$. Calculated %: C 66.83; H 6.33; N 10.64.

1-Carbethoxy-3-(morpholinoacetylamino)-phenoxazine (VIII) was obtained like (VI) and (VII). Yellow platelets from a mixture of benzene and ligroin, m.p. 145°.

Found %: N 10.12. $C_{21}H_{23}O_5N_3$. Calculated %: N 10.59.

Amide of 3-nitrophenoxazine-1-carboxylic acid (X). The acid chloride of 3-nitrophenoxazine-1-carboxylic acid (IX) was shaken with excess concentrated ammonia water at room temperature. After recrystallization from alcohol, dark red prisms with m.p. 218-220°.

Found %: C 57.19; H 3.51; N 15.72. $C_{13}H_9O_4N_3$. Calculated %: C 57.56; H 3.32; N 15.49.

Diethylamide of 3-nitrophenoxazine-1-carboxylic acid (XI). A mixture of 2 g of (IX), 100 ml of dry benzene, and 2.1 ml of diethylamine was heated to boiling for 30 minutes. We obtained 2 g; bright red prisms from a large amount of alcohol, with m.p. 187-188°.

Found %: C 62.20; H 5.12; N 12.95. $C_{17}H_{17}O_4N_3$. Calculated %: C 62.38; H 5.19; N 12.84.

Piperidylamide of 3-nitrophenoxazine-1-carboxylic acid (XII) was obtained as described in the previous experiment. Bright red prisms from alcohol, m.p. 218-220°.

Found %: C 63.85; H 5.12; N 12.23. $C_{18}H_{17}O_4N_3$. Calculated %: C 63.74; H 5.02; N 12.38.

3-Chloroacetyl-10-chloroacetylphenoxazine (XIII). To a solution of 18.3 g of phenoxazine in 250 ml of carbon disulfide at room temperature was added in portions and at the same time 25 g of aluminum chloride and a solution of 22.4 g of chloroacetyl chloride in 70 ml of carbon disulfide. The reaction mixture was stirred for three hours at room temperature, then with boiling for three hours more, and then left over night. After treatment with ice and concentrated hydrochloric acid, the reaction mixture was extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated dry. The residue consisted of yellow crystals. After recrystallization from alcohol, we obtained 11.2 g of (XIII) with m.p. 147-148°.

Found %: C 57.61; H 3.18; N 4.69. $C_{16}H_{11}O_3NCl_2$. Calculated %: C 57.25; H 3.28; N 4.17.

3-Chloroacetyl-10-acetylphenoxazine (XIV) was obtained by the method described in the previous experiment. From 24 g of acetylphenoxazine we obtained 26.3 g of technical (XIV) with m.p. 152-155°. After recrystallization from alcohol, yellow needles with m.p. 159°.

Found %: C 63.34; H 4.02; N 4.79; Cl 11.96. $C_{16}H_{12}O_3NCl$. Calculated %: C 63.70; H 3.93; N 4.65; Cl 11.80.

SUMMARY

1. Acetylation of 1-carbethoxy-3-aminophenoxazine with acetic anhydride led to formation of two substances, 1-carbethoxy-3-acetylamino- and 1-carbethoxy-3-acetylamino-10-acetylphenoxazine, while acylation with chloroacetyl chloride give exclusively the monoacylated derivative, 1-carbethoxy-3-(chloroacetylamino)-phenoxazine.

2. Acylation with chloroacetyl chloride by the Friedel-Crafts method with unsubstituted phenoxazine gave 3-chloroacetyl-10-chloroacetylphenoxazine, and with 10-acetylphenoxazine it gave 3-chloroacetyl-10-acetylphenoxazine.

3. We carried out replacement of chlorine in 1-carbethoxy-3-(chloroacetylamino)-phenoxazine with radicals of diethylamine, piperidine, and morpholine, and in the acid chloride of 3-nitrophenoxazine-1-carboxylic acid replacement with the radicals of ammonia, diethylamine, and piperidine.

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THE FORMATION OF SUBSTITUTED PYRAZOLES IN THE REACTION OF SYDNONES WITH α,β-UNSATURATED NITRILES

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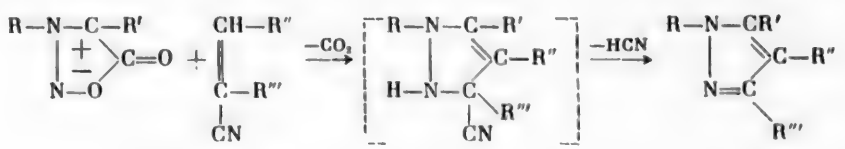
Most characteristic for the sydnones is the reaction of substitution of the hydrogen atom on the carbon in the fourth position of the ring and the splitting of the sydnone ring by the action of acids or alkalis. Several years ago there appeared a report [1] of the reaction of sydnones with 1,4-quinones, leading to the formation of compounds which had, in the opinion of the authors, the structure of indazoquinone derivatives. In the light of known transformations of the sydnones, this reaction seemed somewhat strange and difficult to explain. The reaction of the sydnones with nitriles of α,β-unsaturated acids described in the present paper permits us to conclude that the reaction of the sydnones with quinones is evidently a particular case of the reaction of the sydnones which occurs easily with unsaturated compounds which have activated double bonds.

If we heat 3-phenylsydnone with excess acrylonitrile in the absence of a catalyst in solvents (dioxane, dibutyl ether) or without them, there is evolution of carbon dioxide and hydrogen cyanide and formation of an individual substance which is identified as 1-phenylpyrazole. Thus, on boiling a mixture of 3-phenylsydnone and acrylonitrile (molecular ratio 1 : 10) in dioxane for six hours, we obtained 78.5% 1-phenylpyrazole. By the evolution of carbon dioxide, which was taken up in barium water, we found that below 50° this reaction practically did not occur. In the reaction of acrylonitrile with 3-ethylsydnone under analogous conditions we obtained the 1-ethylpyrazole, undescribed in the literature. In the case of the reaction of 3-phenyl-4-methylsydnone with acrylonitrile it was found that a similar reaction occurred with formation of a substituted pyrazole, and for sydnones with substituents in the fourth position of the ring this occurred with considerably more difficulty. 1-Phenyl-5-methylpyrazole was isolated by heating 3-phenyl-4-methylsydnone with acrylonitrile (solvent, dioxane) for 11 hours with a yield of 20%. In order to study the order of addition of nitriles of α,β-unsaturated acids to sydnones, we carried out the reaction of 3-phenylsydnone with nitriles of methacrylic and crotonic acids. In the case of methacrylonitrile we obtained 1-phenyl-3-methylpyrazole (yield about 56%) whose structure was confirmed by comparison of the constants of its picrate and methiodide with the literature data, and also by a counter synthesis. From crotononitrile and 3-phenylsydnone we obtained 22% of 1-phenyl-4-methylpyrazole, also characterized by the methiodide and picrate.

The results of these experiments permitted us to conclude that the addition of unsaturated conjugated nitriles to sydnone occurs in such a way that the β-carbon atom of the ethylene bond of the nitrile combines with the carbon atom in position four of the sydnone ring, and the α-atom of this bond with the unsaturated nitrogen atom. Then the sydnone ring is split with evolution of carbon dioxide and the corresponding cyanopyrazoline is formed. As is known, such cyanopyrazolines easily split out hydrogen cyanide even with short heating [2] and are converted to the corresponding pyrazoles. Actually, in all cases during the reaction and in less degree on distillation of the reaction products there was evolution of hydrogen cyanide. We did not succeed in isolating a cyanopyrazoline in any experiment.

Thus we can assume that the reaction of sydnones with nitriles of α,β-unsaturated acids occurs as follows.



The suggestion that the intermediate product of this reaction is a cyanopyrazoline is also confirmed by the fact that in the reaction of sydnones with esters of α, β-unsaturated acids we could isolate esters of the corresponding pyrazoline carboxylic acids which were considerably more stable than the corresponding nitriles.*

In the reaction of sydnones with quinones there also occurs addition of the second and fourth atoms of the sydnone ring to the ethylene bond with evolution of carbon dioxide. Then there occurs a shift of a hydrogen atom in the quinone molecule leading to the formation of a hydroquinone structure which under the action of excess quinone is oxidized to the quinone. Both reactions of sydnone, with nitriles of α, β-unsaturated acids and with quinones, in our opinion have very close analogies with the reactions of aliphatic diazocompounds with these substances.

In the reaction of diazomethane and its analogs with unsaturated nitriles and quinones there are also formed pyrazoles and indazoquinones respectively. The deep similarity of the behavior of sydnones and aliphatic diazocompounds in these reactions is indicated by the fact that in the case of the sydnones there occurs the same order of addition of the molecule of unsaturated nitrile as in the aliphatic diazocompounds. For the latter we know the empirical Auwers rule [3] according to which the carbon atom of the diazocompound adds to an electrophilic β-carbon atom of the double bond of an unsaturated conjugated compound.

On the basis of the results which we have obtained we can consider as sufficiently verified the fact that in the reaction of unsaturated nitriles with sydnones (as in the case of the aliphatic diazocompounds, for which this is definitely established [4]) the first and chief step in the process is the addition of a molecule of the nitrile by its electrophilic center (β-carbon atom) to the four carbon atom of the sydnone ring, which has definite nucleophilic properties [5, 6].

Thus we can show that for sydnones a characteristic reaction is not only electrophilic substitution [6], but also a reaction of electrophilic addition, accompanied by rupture of the sydnone ring.

EXPERIMENTAL

Reaction of 3-phenylsydnone with acrylonitrile. We dissolved 4.3 g (0.0266 mole) of 3-phenylsydnone in a mixture of 14 g (0.266 mole) of acrylonitrile and 30 ml of dioxane and boiled until evolution of carbon dioxide stopped (six hours). The reaction was accompanied by evolution of hydrogen cyanide. Dioxane and excess acrylonitrile were distilled off and the residue was distilled in a vacuum. We obtained 3 g (78.5%) of 1-phenylpyrazole.

B.p. 89° (1 mm), d_4^{20} 1.1099, n_D^{20} 1.5960; λ_{max} 254 mμ, log ε 4.141 (in alcohol).

Found %: C 74.50; H 5.71; N 19.26. M (cryoscopic) 149.56. $C_9H_8N_2$. Calculated %: C 74.97; H 5.59; N 19.43; M 144.18.

The literature [7] gives: b.p. 245-246°, d_4^{20} 1.1127, n_D^{20} 1.5966, λ 254 mμ.

Reaction of 3-phenylsydnone with methacrylonitrile. A mixture of 4.6 g (0.0284 mole) of 3-phenylsydnone, 19 g (0.284 mole) of methacrylonitrile, and 30 ml of dioxane was boiled for 35 hours; carbon dioxide and hydrogen cyanide were evolved. The acrylonitrile and dioxane were distilled off and the residue was steam distilled. The reaction product was extracted from the distillate with ether and dried over ignited magnesium sulfate. The residue after distillation of the ether was distilled in a vacuum. We obtained 2.5 g (55.7%) of 1-phenyl-3-methylpyrazole, b.p. 121-126° (9 mm) which crystallized on cooling.

Methiodide. We heated 0.5 g of crystalline 1-phenyl-3-methylpyrazole with an equal weight of methyl iodide in a sealed ampule on a boiling water bath for one hour. The reaction mass crystallized when cooled and was recrystallized from anhydrous alcohol with addition of a small amount of absolute ether. We obtained 0.56 g of methiodide m.p. 140-142°. After repeated recrystallization from anhydrous alcohol, m.p. 141-143°. The literature [8] gives m.p. 144°.

The picrate was separated by long standing of an ether solution of 1-phenyl-3-methylpyrazole and picric acid, m.p. 72.5-73.5° (from dilute methanol). The literature [9] gives m.p. 72-73°.

For identification we synthesized 1-phenyl-3-methylpyrazole from the action of phosphorus pentasulfide on 1-phenyl-3-methyl-5-pyrazolone [10]; the methiodide melted at 140-141.5° and gave no melting point depression mixed with a sample prepared from 3-phenylsydnone.

* The results of a study of the reaction of sydnones with esters of unsaturated acids will be the subject of a future communication.

Reaction of 3-ethylsydnone with acrylonitrile. Twenty-five g (0.219 mole) of 3-ethylsydnone and 23 g (0.435 mole) of acrylonitrile was boiled until evolution of carbon dioxide stopped. Excess acrylonitrile was distilled off and the residue was steam distilled. 1-Ethylpyrazole was extracted from the distillate with ether and dried with ignited magnesium sulfate. After distillation of the ether, the residue was distilled. We obtained 8 g (38%) of 1-ethylpyrazole.

B.p. 136-137°, n_D^{20} 1.4700, d_4^{20} 0.9537; MR_D 28.12; calc. 28.74.*

Found %: C 62.43; H 8.27; N 29.28. $C_5H_8N_2$. Calculated %: C 62.47; H 8.39; N 29.14.

Picrate m.p. 133-134.5° (from alcohol).

Found %: C 40.82; H 3.37; N 21.38. $C_5H_8N_2 \cdot C_6H_2(NO_2)_3OH$. Calculated %: C 40.62; H 3.41; N 21.53.

Methiodide m.p. 97-98° (from acetone).

Found %: I 53.40. $C_6H_{11}N_2I$. Calculated %: I 53.30.

Reaction of 3-phenyl-4-methylsydnone with acrylonitrile. Five g (0.028 mole) of 3-phenyl-4-methylsydnone was dissolved in a mixture of 14.8 g (0.28 mole) of acrylonitrile and 30 ml of dioxane and was boiled for 11 hours. Carbon dioxide and a small amount of hydrogen cyanide were evolved. The excess acrylonitrile and dioxane were distilled off. The residue was a thick oil from which steam distillation followed by extraction of the distillate with ether, drying the ether solution with ignited magnesium sulfate, and distillation yielded 0.9 g (20%) of 1-phenyl-5-methylpyrazole, b.p. 123-127° (7 mm).

Picrate m.p. 97-98.5° (from alcohol).

Methiodide m.p. 257-259° (from alcohol, in a sealed capillary); in an open capillary, decomposes without melting at 279-280°.

The literature [12] gives b.p. 263.5°; picrate m.p. 97-98°; methiodide m.p. 256-257° in a sealed capillary, volatilizes without melting in an open capillary about 290°.

Reaction of 3-phenylsydnone with crotononitrile. A mixture of 3.5 g (0.0216 mole) of 3-phenylsydnone, 14.5 g (0.216 mole) of crotononitrile (b.p. 111-119°, n_D^{20} 1.4220) and 20 ml of dioxane was boiled for 40 hours. Carbon dioxide and hydrogen cyanide were evolved. After distillation of the dioxane and excess crotononitrile, the residue was steam distilled. The distillate was extracted with ether, the ether solution was dried with ignited magnesium sulfate, and the residue after distillation of the ether was vacuum distilled. We obtained 0.75 g of 1-phenyl-4-methylpyrazole (22%), b.p. 118° (5 mm), which after cooling, crystallized.

Picrate m.p. 110-111.5° (from 50% methanol).

Found %: C 49.39; H 3.45; N 18.12. $C_{10}H_{10}N_2 \cdot C_6H_2(NO_2)_3OH$. Calculated %: C 49.62; H 3.38; N 18.08.

Methiodide m.p. 187-188.5° (from alcohol, decomposition).

Found %: C 44.04; H 4.35; I 42.22. $C_{11}H_{13}N_2I$. Calculated %: C 44.01; H 4.36; I 42.28.

The literature [8] gives b.p. 264-266°, methiodide m.p. 160°.

SUMMARY

1. We have found that when sydnones are heated with nitriles of α, β-unsaturated acids in the absence of a catalyst there is condensation with evolution of carbon dioxide and hydrogen cyanide and formation of the corresponding pyrazoles.

2. We have suggested that this reaction of sydnones takes place through a stage of addition of a molecule of unsaturated nitrile to the fourth carbon atom of the sydnone ring with later opening of the ring, evolving carbon dioxide and forming an intermediate unstable cyanopyrazoline which under the conditions of the reaction is converted into the corresponding pyrazole with splitting out of hydrogen cyanide.

* The atomic refraction of the tertiary nitrogen atom was taken equal to 3.46, as this was found empirically for various hydrazole derivatives [11].

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A STUDY OF THE CHEMICAL STRUCTURE OF THE SPONGY POLYMER OF DIISOPROPENYL

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The formation of a spongy polymer of diisopropenyl was first noted by A. I. Kondakov [1]; its chemical structure was studied by Harries [2]. He decomposed the ozonide with water and isolated acetonylacetone, which contained 36% of the carbon skeleton of the polymer. In the residue after distillation of the acetonylacetone he showed the presence of aldehydes and ketoacids, but the nature of these products of the decomposition was not established.

In our work we have set ourselves the problem of studying the chemical structure of the spongy polymer of diisopropenyl obtained by the polymerization of diisopropenyl in a sealed ampule in an atmosphere of nitrogen at 15-18°. The polymer is a nonelastic, friable white product, insoluble in organic solvents and limited in swelling power. Its chemical structure was studied by the method of ozonolysis. Decomposition of the ozonide was carried out with water and by catalytic reduction with a palladium catalyst, deposited on $BaSO_4$, at atmospheric pressure. In the product of water decomposition of the ozonide we determined 49% of the carbon skeleton of the polymer in the form of acetonylacetone and showed the absence of formaldehyde and formic acid, which could have been formed from a portion of the macromolecule arising from addition of a molecule of diisopropenyl in position 1,2. The acetonylacetone was formed in the ozonolysis from the portion of the molecule formed by repeated addition of a diisopropenyl molecule in the 1,4 position. In the product from catalytic reduction of the ozonide in dioxane we found 55.4% of the polymer carbon skeleton in the form of acetonylacetone. We also showed in the ozonization product the presence of acetic acid. Its formation could be explained by abnormal ozonolysis. The carbon atom in the α-position to the double bond could react with ozone with formation of pyruvic acid in the ozonolysis products, and this could split to form acetic acid.

In the spongy polymer we did not find a molecule of diisopropenyl added in position 1,2 and so in the ozonization products di- and triketones were absent; they could have been formed in ozonolysis of portions of structure: $-1,4-1,2-1,4$; $1,4-1,2-1,2-1,4$, and others, and also by branching at the α-methylene group. The residue from distillation of the hydrogenation products was acetonylacetone which partly decomposed during distillation. By elementary analysis it was identical with the residue obtained by distillation of pure acetonylacetone under the same conditions. The results of a study of the products of ozonolysis are given in Table 1.

In catalytic reduction of the ozonide we determined 89.4% of the polymer carbon skeleton formed by addition of the diisopropenyl molecule in position 1,4. This indicates that the spongy polymer of diisopropenyl evidently consists of linear macromolecules bound together by insoluble nuclei.* The insolubility and absence of elastic properties in the spongy polymer of diisopropenyl, like the spongy polymer of divinyl, can be explained by the conditions of its formation [3, 4].

EXPERIMENTAL

The autopolymer of diisopropenyl was obtained by spontaneous polymerization of diisopropenyl in a sealed ampule in an atmosphere of nitrogen at 15-18°. The diisopropenyl used for the polymerization had b.p. 67-68°, n_D^{20} 1.4378, d_4^{20} 1.7210. A long induction period was characteristic of the spontaneous polymerization of diisopropenyl, at the end of which there was a great increase in viscosity of the solution. The duration of the polymerization in the ampule with a primer of spongy diisopropenyl polymer was 13 months. After the same period of time in an ampule

* A necessary condition for the formation of the spongy polymer is the presence in the monomer of an insoluble nucleus, first introduced, or formed during the polymerization.

TABLE 1

Method of decomposing the ozonide	Ozonolysis product	Weight (in g)	% of carbon skeleton in absence	Structure of part from which substance formed	% of diisopropenyl molecule added 1,4
Heated with water	Acetonylacetone	2.47	49.0	−1,4−1,4−	49.0
Catalytic reduction	Acetonylacetone	4.30	55.4	−1,4−1,4−	55.4
	Acetic acid	0.80	6.4	−1,4−1,4−	9.6
	Residue from distillation of ozonolysis products	1.90	24.4	−1,4−1,4−	24.4
			86.2	−	89.4

TABLE 2

Fraction No.	Temperature (pressure in mm)	Weight (in g)	n_D^{20}
1st	35—40° (25)	0.80	1.3780
2nd	89—90 (25)	4.30	1.424
Residue	—	1.90	—

without a primer there had occurred a great increase in the viscosity of the monomer; after introduction of a primer of spongy polymer, the formation of the polymer was complete in four months. The transformation of the diisopropenyl into the spongy polymer went with a great increase in apparent volume. The autopolymer of diisopropenyl had the form of a white, friable mass, easily oxidized in air and therefore all work with it was carried out in an atmosphere of nitrogen. From 37 g of autopolymer of diisopropenyl we extracted 6.3 g (17%) of a rubber like polymer with diethyl; the rest of the autopolymer, which hereafter will be called the spongy polymer, was a white, friable substance, lacking elastic properties, and practically insoluble in organic solvents.

Found %: C 86.21, 86.29; H 12.24, 12.17. $(C_6H_{10})_x$. Calculated %: C 87.81; H 12.19.

Ozonization was carried out in chloroform at -30° with ozonized oxygen which contained 5-6% ozone, in an apparatus which assured a constant ozone concentration [5]. In each experiment we ozonized 2 g of polymer. Addition of ozone took place at the same rate and corresponded to addition of 1.23 g mole of ozone, or 105% calculated on the double bonds of the polymer. The amount of ozone added was determined from the absorption curve which was drawn at the same time as the ozonization process. The spongy polymer of diisopropenyl was ozonized completely in chloroform, forming a clear, colorless solution of the ozonide. After distillation of the chloroform, the ozonide remained as a colorless, viscous substance. Decomposition of the ozonide was carried out by heating with water and by catalytic reduction with a catalyst of Pd on $BaSO_4$ at atmospheric pressure in dioxane. For quantitative determination of acetonylacetone in the decomposition products of the ozonide, we first obtained acetonylacetone by saponification of diacetylsuccinic ester and chose a method for determining it quantitatively.

The boiling point of acetonylacetone was 89-90° at 25 mm, n_D^{20} 1.427. The literature gives for acetonylacetone b.p. 89-90° at 25 mm, n_D^{20} 1.428, n_D^{20} 1.423 [6]; n_D^{20} 1.4441 [7].

Derivatives of acetonylacetone have been obtained with hydrazine hydrate [7], 2,4-dinitrophenylhydrazone [8], and phenylhydrazine [9]. To a threefold excess of phenylhydrazine we added 10 ml of water and acetic acid, then added the sample of acetonylacetone, and heated for 5-10 minutes on a water bath. The precipitate was treated with 4-5 drops of concentrated sulfuric acid, and steam distillation was carried out. The resulting 1-phenylamino-2,5-dimethylpyrrole was filtered and dried to constant weight in a vacuum desiccator. M.p. 91° [9].

Found %: C 77.18, 77.39; H 7.70, 7.66; N 15.14, 15.09. $C_{12}H_{14}N_2$. Calculated %: C 77.42; H 7.53; N 15.05.

The yield of 1-phenylamino-2,5-dimethylpyrrole was 71%. The derivatives of acetonylacetone with hydrazine hydrate and 2,4-dinitrophenylhydrazine were obtained in lower yield.

Decomposition of the ozonide of the spongy diisopropenyl polymer by water. We ozonized 3.7 g of polymer containing 3.2 g of carbon, in chloroform. We obtained 5.85 g of ozonide which was decomposed by heating with water. In 34.35 g of water soluble decomposition products of the ozonide we determined the acetonylacetone quantitatively by the reaction with phenylhydrazine. From 4.62 g of the water solution we obtained 0.3856 g (71%) of 1-phenylamino-2,5-dimethylpyrrole. M.p. 90-91°, % N 15.21. Calculated on 100% yield we obtained 0.5430 g which corresponds to 0.3329 g of acetonylacetone. In all, the water solution of the ozonolysis product contained 2.47 g of acetonylacetone, or 49% of the carbon skeleton of the ozonized spongy diisopropenyl polymer. Formic acid and formaldehyde were not detected in the ozonolysis products of spongy diisopropenyl polymer [10, 11].

Catalytic reduction of the ozonide from spongy diisopropenyl polymer in dioxane. We ozonized 5.7 g of polymer (containing 4.9 g of carbon) in chloroform. The solvent was distilled off at 18 mm and 20°. The ozonide was dissolved in dioxane (b.p. 101°, n_D^{20} 1.4213; reaction for peroxide negative). Catalytic reduction of the ozonide was carried out in the apparatus of S. V. Lebedev [12]. In the reduction we used 2 g of catalytic Pd on $BaSO_4$ per 1 g of ozonized polymer. Fischer shows that the catalytic reduction of ozonides with this catalyst leads to aldehydes and ketones [13]. At 14° (760 mm) we used 1800 ml of hydrogen in reduction of the ozonide (1713 ml at 0° and 760 mm) which corresponds to 91% of the calculated value.* The solution of hydrogenation products in dioxane gave a negative reaction for ozonides and peroxides. The solvent was distilled off at 20° (25 mm) and the hydrogenation products were distilled (Table 2).

The first fraction had an acid reaction to litmus and a negative reaction with phenylhydrazine.

Found %: C 39.89; H 6.47. $C_2H_4O_2$. Calculated %: C 40.00; H 6.67.

We obtained the silver salt.

Found %: Ag 63.92, 64.00. $C_2H_3O_2Ag$. Calculated %: Ag 64.00.

On the basis of the analysis we consider that the first fraction is acetic acid formed by decomposition of pyruvic acid. In it we determined 6.4% of the carbon skeleton of the ozonized spongy polymer.

From the second fraction we obtained a derivative with phenylhydrazine, 1-phenylamino-2,5-dimethylpyrrole, m.p. 91°.

Found %: C 77.20, 77.33; H 7.68, 7.62; N 15.16, 15.10. $C_{12}H_{14}N_2$. Calculated %: C 77.42; H 7.53; N 15.05.

The analysis is identical with that for pure acetonylacetone and shows that this fraction is acetonylacetone. In the acetonylacetone which we isolated and characterized there was 55.4% of the carbon skeleton of the ozonized polymer.

In the residue which remained after distillation of the products of catalytic reduction of the ozonide, we determined %: C 59.63, 59.65; H 7.77, 7.90. In the residue after distillation of pure acetonylacetone under the same conditions we determined %: C 59.87; H 8.25. The calculated values for $C_6H_{10}O_2$ %: C 63.15; H 8.78. The residue obtained in distillation of the products of catalytic reduction of the ozonide of the spongy diisopropenyl polymer was identical in analysis with the residue obtained in distillation of pure acetonylacetone and thus is acetonylacetone partly decomposed by heating. It contained 24.4% of the carbon skeleton of the ozonized polymer. In all the products of catalytic reduction of the ozonide of the spongy polymer in dioxane we found 89.4% of the carbon skeleton of the polymer studied.

SUMMARY

1. We have shown that the spongy diisopropenyl polymer is formed by addition of diisopropenyl molecules in the position −1,4−1,4−.

2. Among the products of ozonolysis of the spongy diisopropenyl polymer we have found no substances which would indicate a branched structure for this polymer.

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STUDIES IN THE FIELD OF COMPOUNDS WHICH CONTAIN A THREE MEMBER OXYGEN RING

XXVII. THE REACTIONS OF ETHYL ESTERS OF SOME β-DISUBSTITUTED GLYCIDIC ACIDS WITH HYDRAZINE HYDRATE

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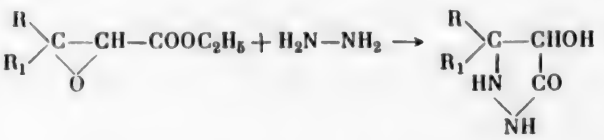
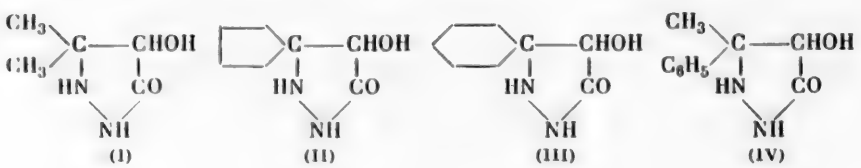
The reaction of esters of glycidic acids with hydrazine hydrate, to judge from the literature, has not yet been studied by anyone. We could expect here the formation of a hydroxypyrazolidone ring, since in esters of glycidic acid there are two reactive centers, the oxide ring and the ester group which, as the equation shows, should give 3-disubstituted 4-hydroxy-5-pyrazolidones.



Compounds of the type are still undescribed, except for 2,3-diphenyl-4-hydroxy-5-pyrazolidone. The latter was obtained by reaction of the ethyl ester of β-phenylglycidic acid with phenylhydrazine [1]. The reaction has also been described of phenylhydrazine with the ethyl ester of β-dimethylglycidic acid [2], but the structure of the reaction product is not reported.

We have carried out the reaction of hydrazine hydrate with four esters of glycidic acids: the ethyl esters of β-dimethylglycidic acid, β-tetramethylene- and β-pentamethyleneglycidic acids, and β-methyl-β-phenylglycidic acid. The reaction in all cases was carried out by heating equimolecular amounts of the components in an open flask on a boiling water bath. As a result we obtained the 4-hydroxy-5-pyrazolidones whose formulas are given below.



(I) (II) (III) (IV)

The yield of products given in the experimental, part was calculated starting from 100% of the starting ester of glycidic acid. Actually this is not accurate. According to our preliminary data, in the synthesis of glycidic esters according to Darzan, there is obtained a considerable amount of impurity which is difficult to separate, and which sometimes reaches 40%. Therefore the percent yield of hydroxypyraolidones which we give is low.

EXPERIMENTAL

3-Dimethyl-4-hydroxy-5-pyrazolidone (I). Ten g of ethyl β-dimethylglycidate and 3.4 g of hydrazine hydrate (first distilled) were heated in an open flask for 30 minutes on a boiling water bath. After cooling to room temperature the contents of the flask crystallized completely. After recrystallization from alcohol we obtained 5 g of a colorless crystalline compound (56%). M.p. 170°.

Found %: C 46.08; H 7.75; N 21.44. $C_5H_{10}O_2N_2$. Calculated %: C 46.15; H 7.69; N 21.53.

3-Tetramethylene-4-hydroxy-5-pyrazolidone (II). Five g of ethyl β-tetramethyleneglycidate and 1.5 g of hydrazine hydrate were heated for 30 minutes on a boiling water bath. Even during heating the reaction mass crystallized. After cooling and recrystallization from alcohol we obtained 2.4 g of a colorless crystalline compound (52%). M.p. 184-185°.

Found %: N 17.81. $C_7H_{12}O_2N_2$. Calculated %: N 17.94.

3-Pentamethylene-4-hydroxy-5-pyrazolidone (III). Five g of ethyl β-pentamethyleneglycidate and 1.35 g of hydrazine hydrate were heated on a boiling water bath for 20 minutes. The reaction mass crystallized completely when cooled. After recrystallization from alcohol we obtained 2.1 g of colorless crystals (45.6%). Yield 128-130°.

Found %: N 16.65. $C_8H_{14}O_2N_2$. Calculated %: N 16.47.

3-Methyl-3-phenyl-4-hydroxy-5-pyrazolidone (IV). Five g of ethyl β-methyl-β-phenylglycidate mixed with 1.2 g of hydrazine hydrate was heated in an open flask on a boiling water bath for one hour. On the next day the reaction mass had completely crystallized. After three recrystallizations from alcohol we obtained 1.6 g of colorless powdery substance (35%). M.p. 109-111°.

Found %: N 14.24. $C_{10}H_{12}O_2N_2$. Calculated %: N 14.58.

SUMMARY

1. We have studied the reaction of some esters of β-disubstituted glycidic acids with hydrazine hydrate. We have shown that here there is formation of 3-disubstituted 4-hydroxy-5-pyrazolidones.

2. We have obtained and characterized four undescribed hydroxypyrazolidones.

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STUDIES IN THE FIELD OF RHODAMINE DYES AND COMPOUNDS RELATED TO THEM

I. THE SIMPLEST RHODAMINE – ITS PREPARATION AND PROPERTIES

I. S. Ioffe and V. F. Otten

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 5,
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Original article submitted June 7, 1960

The simplest of the rhodamine dyes, which in one of the tautomeric forms is ascribed the structure of 3,6-diaminofluorane (I) has not been sufficiently studied. It was first mentioned in a German patent of 1887 [1]; in 1899 a detailed paper was devoted to this dye by R. Meyer and W. Sundmacher [2]. In the recent literature there are no further remarks on this dye. To obtain rhodamine, the authors used the method described in the patent of condensation of m-aminophenol with phthalic anhydride in the presence of concentrated sulfuric acid. When the melt was poured into water it formed a copious precipitate which was assumed to be rhodamine sulfate. When it was treated with sodium acetate it gave the free dye; after a number of crystallizations from water it was isolated in very small yield in the pure state, in the opinion of the authors, as a microcrystalline, dark red substance which softened at 230° with later melting at 250-252°. The dye obtained in this way, according to the authors of the paper, was soluble in both acids and alkalis.

However, in an experimental test of the work of Meyer and Sundmacher, we became convinced that the substance isolated by these authors and assumed by them to be an analytically pure rhodamine, was actually a mixture of several substances. Most convincing here was paper chromatography of the substance. On the chromatogram, shown schematically in Figure 1, right, three spots are apparent which differ in color and height of rise. Such a chromatogram is obtained unchanged after repeated recrystallizations of the dye from water. After numerous attempts to establish the purity of the dye using a chromatographic control we succeeded in obtaining the desired rhodamine in pure form. In its chromatography (Fig. 1, left) we obtained only one spot, which in height of rise and color corresponded to one of the three substances found in the "rhodamine" of Meyer and Sundmacher. When we studied the properties of the compound in detail, we worked out a simpler method for purifying the dye which is described in the experimental part. The structure of the resulting substance was confirmed by analysis, and also by converting it into fluorescein, identified as its acetyl derivative. For this purpose we used diazotization with later decomposition of the bisdiazo derivative as described in the experimental part.

This shows that Meyer and Sundmacher could not separate the rhodamine which they obtained from the other reaction products which accompanied it. Therefore the data on the properties of rhodamine given in the paper of these authors [2] and reflected in the handbook literature is incorrect. We have shown that pure rhodamine melts considerably higher, at 342-344° and its acetyl derivative, for which the literature gives m.p. 170-173°, actually melts at 308-310°.

The data of Meyer and Sundmacher on solubility of rhodamine in alkali are also incorrect. We have shown that pure rhodamine has small solubility (about 60 mg/liter) in water and in aqueous alkali, with the same intensity of color, orange, in such solutions, with a bright yellow-green fluorescence. Figure 2, which gives the absorption curve for the dye in a neutral medium, in 0.1 N and in 1 N solutions of sodium hydroxide, clearly shows the complete identity of these curves.

In Figure 2 we give curves for absorption of rhodamine solutions in a greater concentration, 2.7 N alkali. Here the solution is less intensely colored, but does not change the character of the absorption curve nor the position of the maximum, but only decreases its height. We show that the intensity of the color gradually changes on standing in 1 N alkali solution, as Figure 3 indicates. When the alkali is neutralized, the previous color is restored. It follows from this that the dye under the action of concentrated alkali is reversibly converted into a colorless substance, whose presence is not shown in the absorption in the visible part of the spectrum.

Rhodamine dissolves best in an acid medium, this showing weakly basic properties. With weak acids such as acetic, rhodamine does not form salts; it gives relatively stable salts with strong acids, whether mineral, or organic (oxalic, picric); here the saturated solutions have an orange-red color which passes into yellow on dilution and has an intense yellow green fluorescence. Salts of rhodamine with strong acids are isolated by cooling hot concentrated acid solutions, but when dissolved in water they undergo hydrolysis.

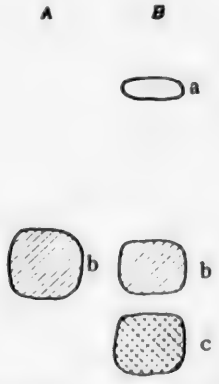


Fig. 1. Schematic paper chromatogram. A) For the substance obtained by the authors; B) for the substance obtained by the method of Meyer and Sundmacher [2]. Color of spots: a) Yellow; b) orange; c) crimson.

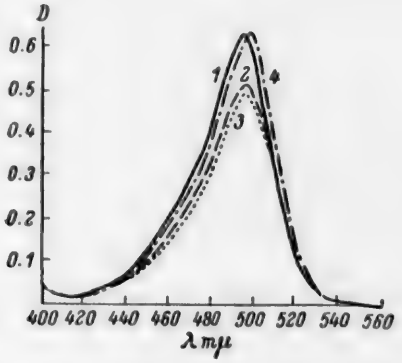


Fig. 3. Change in absorption of rhodamine in 1 N NaOH with time. 1) Starting; 2) after 5 minutes; 3) after 10 minutes; 4) after acidification.

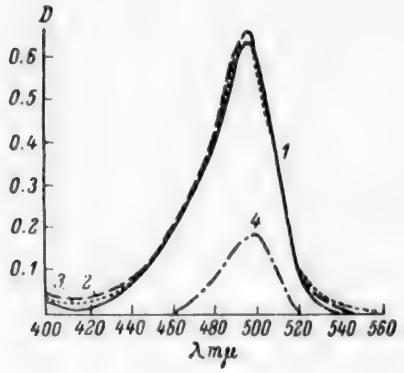


Fig. 2. Absorption curves of rhodamine in the alkaline region. 1) H_2O; 2) 0.1 N NaOH; 3) 1 N NaOH; 4) 2.7 N NaOH.

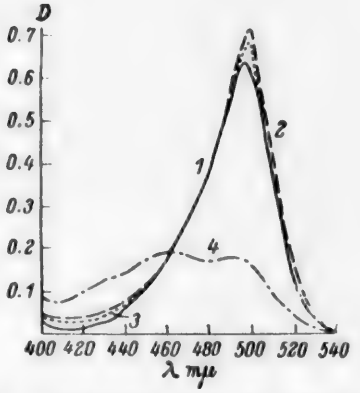
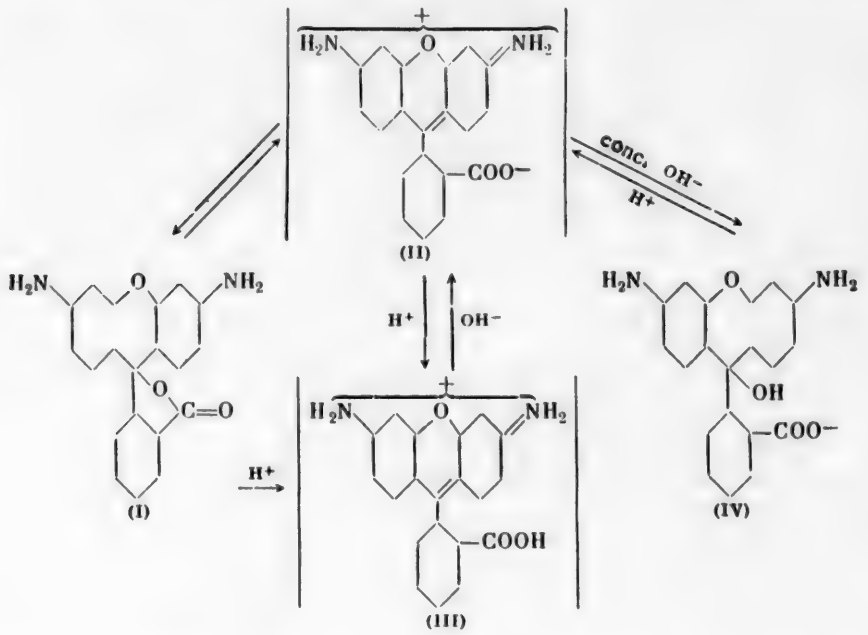


Fig. 4. Absorption curves for rhodamine in the acid region. 1) H_2O; 2) 0.1 N HCl, H_2SO_4; 3) 1 N HCl, H_2SO_4; 4) 10 N HCl, H_2SO_4.

In spite of the presence in the rhodamine molecule of two amino groups, it forms salts with one equivalent of acid. Only when the dye is dissolved in strong acids, such as 10 N hydrochloric or sulfuric is there a marked change in color which is probably the result of forming the ion of a two-acid salt; on dilution of such solutions with water, as a result of stepwise hydrolysis, there is restoration of the orange color characteristic of the rhodamine salt with one equivalent of acid. In Figure 4 we show the curve for absorption of dilute solutions of rhodamine in water, in 0.1, 1, and 10 N hydrochloric and sulfuric acids.

Comparison of the absorption curves of Figures 2 and 4 shows that the color of the dye in the pH range from 0.1 to 14 is not changed. In all cases the nature of the curve and the position of the absorption maximum remain unchanged. This indicates that with change in pH of the medium over such a wide interval the fine chemical structure of the dye is not destroyed.

The color and behavior of rhodamine at different pH values can be explained if we assume that in a neutral medium it is a dipolar ion (II), in which the negative charge is concentrated on the carboxyl group and the positive charge, as in the bases of the triphenylmethane dyes, is distributed between both amino groups and the atoms of the xanthine grouping which share jointly with the amino groups in the formation of a system of conjugated bonds.



Under the influence of acids such a dipolar ion could add one proton to the carboxyl group with formation of the complex cation (III). This could explain the ability to form a relatively stable salt with one equivalent of acid. Also, since the addition of a proton to the carboxyl group would not change the electron structure which determines the color of the compound, the color of the dye would remain unchanged in going from a neutral medium into the acid region (Fig. 4). The ability to add one more proton due to the unshared electron pair of the nitrogen atoms of the amino groups or the oxygen of the heterocyclic grouping is weakened as a result of the delocalization of the positive charge; therefore, the ion of the dibasic salt of rhodamine can be obtained only by more energetic attack of protons in concentrated acids. Here already the electron structure of the dye is changed, upon which the increased color of the solution shown in Figure 4 depends. This doubly charged salt is little stable and when the solution is diluted with water, is hydrolyzed with formation of the deeper colored ion (III).

These ideas on the structure of rhodamine permit us to explain the insolubility of the dye in alkalis, which we observed to contradict the literature data. In this compound, as a result of the delocalization of the positive charge, the ability to split off protons from either amino group is weakened. Therefore even at pH of 13 the concentration of hydroxyl ions is not sufficient to split off the protons and destroy the electron structure of the dye, so that its solubility is not changed and the color remains as in the alkali solution.

With more active attack of the hydroxyl ions in more concentrated sodium hydroxide solutions there is a transformation of the dye leading to the decolorizing of the dye shown in Figures 2 and 3. Since with acidification the solution decolorized by alkali quickly returns to the colored form of the dye, such decolorizing probably depends on addition of the hydroxyl group to the resulting anion of the corresponding carbinol derivative (IV), which exists only in a strongly alkaline solution.

The internal ester (lactone) of this carbinol derivative, 3,6-diaminofluorane (I), is also unstable. As our experiments showed, it is formed on heating the free dye in some nonpolar solvents. Here there is obtained a colorless solution, but on cooling, the base is again formed in the colored state. The lactone form (I) can be fixed only in some rhodamine derivatives, especially in acetylation, which will be described in one of the following communications.

EXPERIMENTAL

Preparation of rhodamine. Condensation of m-aminophenol with phthalic anhydride. In a round-bottomed flask we added to 100 ml of concentrated sulfuric acid, 25 g of m-aminophenol, and 20 g of phthalic anhydride. The mixture was heated on an oil bath at 180-190° for four hours. After cooling the resulting thick black liquid was poured in small portions, with stirring, into 400 ml of water with ice; the copious red-brown precipitate of crude sulfate of the dye was filtered off and washed with a small amount of water. In its composition, besides rhodamine, was a considerable amount of more basic substance, better soluble in acid, and also an alkali soluble substance of acid character as well as tarry products formed in the reaction.

Isolation of rhodamine. For separation of the products with an acid character the crude sulfate of the dye was treated with an excess of strong ammonia solution and allowed to stand over night, after which it was filtered through a thick filter and washed with water until the odor of ammonia disappeared. (The filtrate was kept for isolation from it, of the acid dye which accompanied rhodamine; this will be the subject of a future communication.) The precipitate on the filter after drying weighed 13-15 g and contained about 60% rhodamine. It was heated to boiling in 700-800 ml of 0.3 N hydrochloric acid and filtered through a heated funnel; the precipitate was washed with 200 ml of hot 0.3 N hydrochloric acid; on the filter remained carbonaceous products of tarring. From the combined filtrates on cooling there precipitated beautiful bronze scales of rhodamine hydrochloride which were filtered off and dried. The resulting product, which weighed about 8 g, already contained up to 90% rhodamine.

Purification of rhodamine. Eight g of the above described hydrochloride of the dye was treated with 200 ml of 5% sodium hydroxide solution. The resulting finely crystalline precipitate with the crimson color of the dye base was filtered off through a thick filter and washed with water to a pale yellow color in the wash water. Then the precipitate was heated with 80 mg of 0.3 N hydrochloric acid. Here only a small part of the precipitate, containing chiefly substances of a more basic character, dissolved. The main mass of the dye remained in the precipitate. It was filtered and crystallized from 800 ml of 0.3 N hydrochloric acid with addition of activated charcoal. The resulting precipitate of the hydrochloride was again treated with a 5% solution of sodium hydroxide and the base once more recrystallized from 0.3 N hydrochloric acid with separation of the first hydrochloride fraction, enriched by admixture of more basic substances. This purification was repeated three to four times until a chromatographically pure substance was obtained.* As a final total we obtained about 6-7 g (20%) (calculated on the m-aminophenol taking part in the reaction). For analysis we used chromatographically pure rhodamine dried to constant weight at 150°.

Found %: C 73.08, 73.50; H 4.13, 4.23; N 8.54, 8.50. $C_{20}H_{14}O_3N_2$. Calculated %: C 72.72; H 4.27; N 8.48.

By crystallization from 0.3 N hydrochloric acid we obtained the salt of rhodamine with one equivalent of acid.

Found %: C 66.06, 66.01; H 4.74, 4.69; N 7.84, 7.98; Cl 9.87, 10.03. $C_{20}H_{15}O_3N_2Cl$. Calculated %: C 65.48; H 4.12; N 7.64; Cl 9.68.

Rhodamine base occurs as a crimson powder with a silvery glint. On rapid heating it melted at 342-344° (with decomposition); with slow rise in temperature the substance decomposed without melting beginning from 320°. Free rhodamine was practically insoluble in water and alkali. In a saturated solution at 20° the concentration of dye was about 0.006%. It was very slightly soluble in alcohol (about 0.015%), acetone, or acetic acid; somewhat better on heating. When boiled in benzene, toluene, or xylene, rhodamine base partly dissolved with formation of a colorless solution. On cooling, it precipitated again as crimson flakes of the base with m.p. 341-343°. The dye was better soluble in strong acids, forming the single acid salt, which was salted out by excess acid. Salts of mineral acids from rhodamine decomposed above 380° without melting. They dissolved much better than rhodamine itself in polar solvents, but were not soluble in nonpolar solvents. All the solutions of the dye in polar solvents were orange red with a yellow-green fluorescence, which was strengthened by moderate dilution.

Acetylation. Five g of rhodamine base and 40 ml of acetic anhydride were heated for 20-30 minutes on a water bath and then the reaction mass was poured into 200 ml of cold water and the light, fine precipitate of the acetyl derivative was filtered off. The weight of dry product was 5.1 g (80%). Recrystallization from 40% alcohol with activated charcoal gave a colorless product with m.p. 308-310°.

Found %: N 6.80, 6.58. $C_{24}H_{18}O_3N_2$. Calculated %: N 6.76.

* For a chromatographic control we used a one dimensional ascending paper chromatogram, using as solvent a 0.5% water solution of sodium hydroxide (see, for example [3]).

Acetyl rhodamine was soluble in alcohol, acetone, ether, and acetic acid, insoluble in water. Acids and alkalis saponified it to the starting rhodamine.

Conversion of rhodamine into fluorescein. We dissolved 3.5 g of rhodamine in 30 ml of concentrated sulfuric acid and gradually added to this a solution of nitrosylsulfuric acid (prepared by dissolving 1.5 g of $NaNO_2$ in 20 ml of concentrated sulfuric acid. After stirring for half an hour at room temperature, the mixture was poured into 0.5 liter of water and the resulting dark red solution of the bisdiazo derivative was heated. Nitrogen was evolved, the solution became yellow and a brown, flaky precipitate began to come down. This precipitate was filtered off, washed with water, and dried. From it, by heating with acetic anhydride we obtained an acetyl derivative which after crystallization from 40% alcohol with activated charcoal gave light yellow crystals with m.p. 205-207°. A sample mixed with the analogously obtained acetyl derivative of known fluorescein gave no melting point depression.

SUMMARY

1. We have established that the dye obtained by condensation of m-aminophenol with phthalic anhydride and described in the literature as the simplest of the rhodamine dyes unsubstituted rhodamine, actually is a mixture of several dye substances which are not separated by crystallization from water as recommended in the literature.

2. We have worked out a process for purifying rhodamine which permits its isolation in individually pure state. The most suitable criterion of purity of the dye is paper chromatography. The structure of the substance has been confirmed by analysis and is shown by its conversion to fluorescein.

3. Unsubstituted rhodamine, in contradiction to the literature report, does not dissolve in alkali, but reacts with strong acids to give a salt with one equivalent of the acid.

4. In neutral and weakly alkaline media rhodamine can be considered as a dipolar ion which in acid media without change in electron structure forms a complex cation. The spectral characteristics of rhodamine do not change over a wide range from pH 0.1 to pH 14.

5. The electron structure of the dye is destroyed by the action of strong acids or alkalis with formation in the first case of a more highly colored cation of the salt with two equivalents of acid, and in the second of a colorless anion, probably corresponding to a carbinol derivative.

6. In the acetylation of rhodamine there is formed an acetyl derivative of a lactone colorless form of the dye.

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A METHOD FOR PREPARING FLUORINE DERIVATIVES OF PHOSPHORUS

A. Ya. Yakubovich, V. A. Ginsburg, and S. F. Makarov

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Original article submitted May 23, 1960

We have previously shown that in the reaction of some carboxylic acid fluorides with alkoxyl derivatives of Si, Sn, and S there is replacement of the alkoxy group by fluorine and formation of fluorine derivatives of these elements by the scheme [1].

$$R_m El^n (OR')_{n-m} + CH_3COF \longrightarrow R_m El^n (OR')_{n-m-1}F + CH_3COOR'$$

In using this conversion in a series of alkoxy derivatives of antimony [2] we obtained the corresponding fluorine derivatives of antimony. It seemed of interest to extend the use of this reaction to the phosphorus compounds, which is done in the present work in the case of some available derivatives of pentavalent phosphorus, the esters of alkylphosphonic acids.

As was shown, when a mixture of acetyl fluoride with the corresponding alkoxy derivative of pentavalent phosphorus was heated at about 150° there was smooth replacement of the alkoxyl group by fluorine and formation of esters of alkylfluorophosphonic acid by the scheme.

$$RPO(OR')_2 + CH_3COF \longrightarrow RPO(OR')F + CH_3COOR'.$$

The obtaining of positive results in the addition of fluorine to phosphorus by reaction of alkoxy derivatives of the latter with acetyl fluoride (as in the example given above) shows the general character of this reaction in a number of organic compounds of the elements and it can obviously be widely used in preparative chemistry.

EXPERIMENTAL

Ethyl ester of ethylfluorophosphonic acid. A mixture of 8 g (1 mole) of diethyl ester of ethylphosphonic acid and 4 g (1.3 mole) of acetyl fluoride was heated for four hours in a flask at 140-150°. Ethyl acetate was distilled off at atmospheric pressure and the residue was distilled in a vacuum. Yield of ester with b.p. 55-56° (7 mm) and d_{20}^{20} 1.1333 was 5.5 g (72%).

Found %: F 11.83, 11.51; OC_2H_5 29.26, 29.60. $C_4H_{10}O_2PF$. Calculated %: F 11.85; OC_2H_5 28.20.

Ethyl ester of bromomethylfluorophosphonic acid. A mixture of 2.4 g (1 mole) of diethyl ester of bromomethylphosphonic acid and 0.8 g (1.3 mole) of acetyl fluoride was heated for eight hours in a sealed ampule at 140°. On distillation we obtained 1.2 g of ester with b.p. 84-85° (6 mm) and d_{20}^{20} 1.4584.

Found %: F 8.37, 8.35. $C_3H_7O_2PFBr$. Calculated %: F 9.24.

Ethyl ester of trichloromethylfluorophosphonic acid. A mixture of 8.4 g (1 mole) of diethyl ester of trichloromethylphosphonic acid and 2.25 g (1.1 mole) of acetyl fluoride was heated in an ampule under the conditions described above. We observed tarring when the mixture was distilled. Besides ethyl acetate we obtained 2.5 g ester, b.p. 87° (13 mm), d_{20}^{20} 1.51017.

Found %: F 8.17, 7.84; OC_2H_5 19.87, 20.24. $C_3H_5O_2PFCl_3$. Calculated %: F 8.27; OC_2H_5 19.65.

SUMMARY

We have showed that on heating alkoxyl derivatives of phosphorus with acetyl fluoride there is disproportionation leading to formation of the fluoride of the corresponding phosphorus acid and an alkyl acetate.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

STUDIES IN THE FIELD OF CONJUGATED SYSTEMS

CXXXV. THE DIRECTION OF ADDITION OF ALKYL HYPOBROMITES AND LITHIUM ALKYLS TO VINYLPROPENYLACETYLENE*

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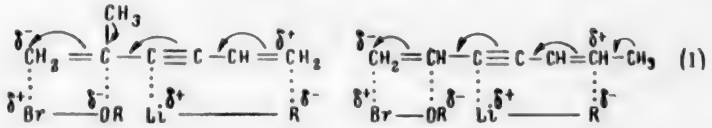
pp. 1518-1524, May, 1961
Original article submitted May 24, 1960

Divinylacetylene under the action of benzene sulfodibromoamide in alcohol solution adds hypobromites in the well known electrophilic way at one of the two uniform double bonds [1]. Lithium alkyls add to the same hydrocarbon in the 1,4 position and negatively polarized alkyls go to the end carbon atom [2]. The unsymmetrical diene, vinylisopropenylacetylene adds alkyl hypobromites at the isopropenyl group [1] and lithium alkyls at the vinyl group with formation of isopropenylalkylallenes [3].

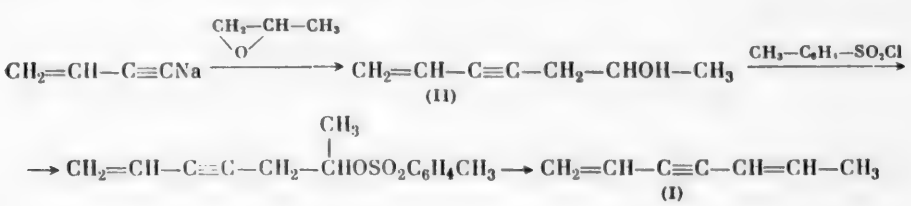
In order to explain the reason for the difference in direction of addition of alkyl hypobromites and lithium alkyls to vinylisopropenylacetylene, and also to explain the mechanism of addition of lithium alkyls to unsaturated compounds it was necessary to study the direction of addition of such substances to vinylpropenylacetylene (I).



If in both cases there is a heterolytic process, then the electronic configuration of the molecule should first act on the place of initial attack. Hence also in the case of vinylpropenylacetylene, which is considerably more polar than is vinylisopropenylacetylene,** addition of alkyl hypobromites and lithium alkyls should go on different double bonds.

If the reaction of lithium alkyls with hydrocarbons is a homolytic process, then the direction of their addition will first be determined by steric conditions, and then they will add to vinylpropenylacetylene in the same way as do the alkyl hypobromites, at the unsubstituted vinyl group.

Vinylpropenylacetylene is not described in the literature. We obtained a mixture of its cis- and trans-forms by dehydration of vinylacetylenyl alcohol (II) through the tosyl ester. Vinylacetylenyl alcohol (II) was obtained by the action of propylene oxide on sodium vinylacetylide in liquid ammonia.



* Dienes. V.

** Vinylpropenylacetylene has a dipole moment 0.78 D (measured in our laboratory by K. S. Mingaleva), vinylisopropenylacetylene has 0.61 D [4].

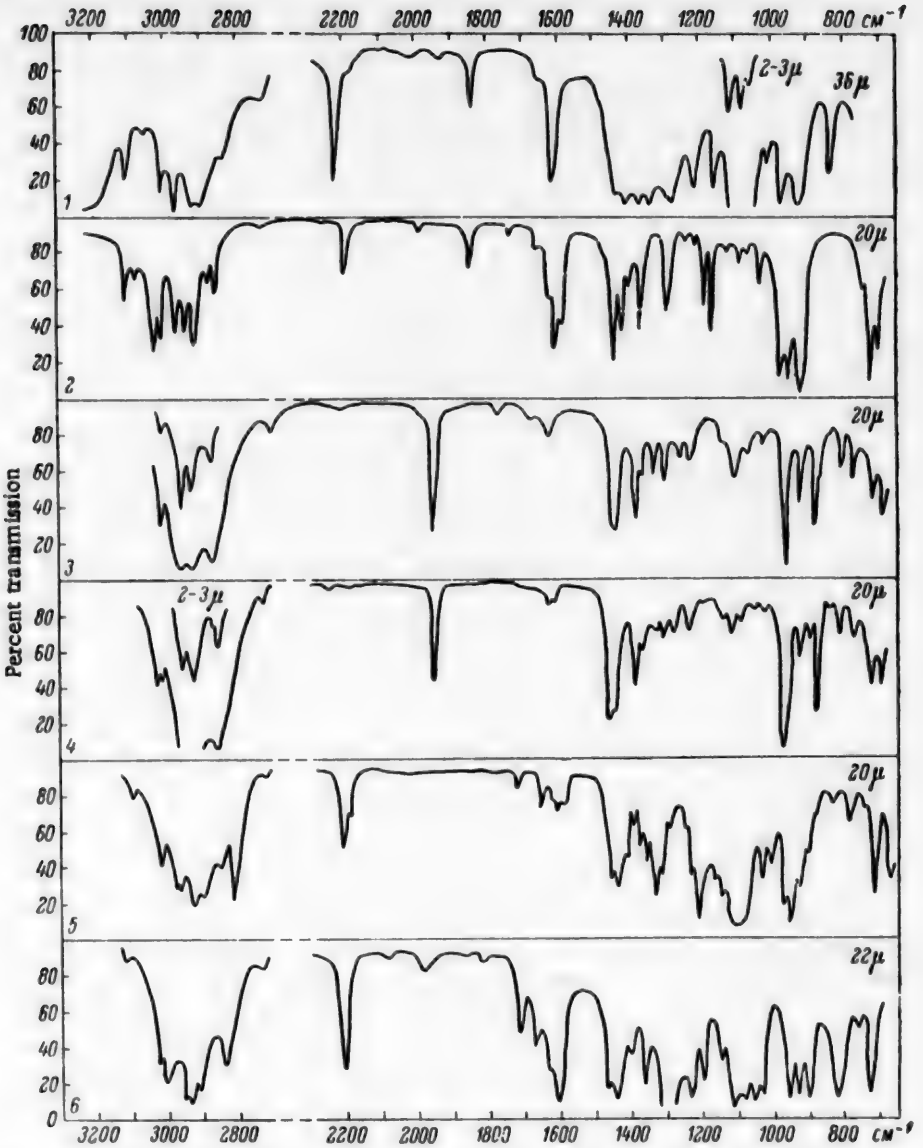


Fig. 1. Infrared transmission spectra. 1) 1-Hepten-3-yn-6-ol; 2) 1,5-heptadien-3-yne; 3) 2,4,5-nonatriene; 4) 2,4,5-undecatriene; 5) addition product of methyl hypobromite to 1,5-heptadien-3-yne; 6) dienyne ethers obtained by dehydrobromination of the bromo-ethers.

The structures of the alcohol (II) and the hydrocarbon (I) assumed from the method of synthesis were confirmed by the infrared spectra.

In the infrared spectrum of alcohol (II) (Fig. 1, curve 1) are the characteristic frequencies of the vinyl group 3100, 1608, 971, and 933 cm^{-1} and the triple bond, 2226 cm^{-1}. In the infrared spectrum of hydrocarbon (I) the vinyl group shows the frequencies 3103, 1586, 1603, 971, and 918, the propenyl group 1620 and 951 cm^{-1}. Frequencies which could indicate any other structure for alcohol (II) and hydrocarbon (I) than those shown in the scheme were absent.

When hydrocarbon (I) was hydrogenated over $Pd/CaCO_3$ it gave n-heptane (identified by constants and infrared spectrum).

By the action of benzenesulfodibromoamide on a solution of vinylpropenylacetylene (I) in methyl alcohol we obtained in small yield a mixture of bromoethers with considerable predominance of (III). Addition at the triple bond or in the 1,4 position practically did not occur.

$$(I) \longrightarrow \underset{(III)}{CH_2Br-CH(OCH_3)-C\equiv C-CH=CH-CH_3} \xrightarrow{KOH} \longrightarrow \underset{(IV)}{CH_2=C(OCH_3)-C\equiv C-CH=CH-CH_3} \xrightarrow{H_2O} CH_3-CO-C\equiv C-CH=CH-CH_3 \xrightarrow{[H_2]} \rightarrow CH_3-CO-C_5H_{11}$$

The conclusion of the chief direction of addition of methyl hypobromite to hydrocarbon (I) was mainly drawn on the basis of comparison of infrared spectra of the bromoether and the starting hydrocarbon. In the bromoether spectrum there was retention of the intense frequency of the acetylene bond (2215 cm^{-1}) and absence of the characteristic frequency of the allene group (about 1950 cm^{-1}). The frequency of the vinyl group was weakened. The intensity of the frequency of the group $-CH = CH-$ (952 cm^{-1}) was not changed. Hence, addition occurred preferably on the vinyl group.

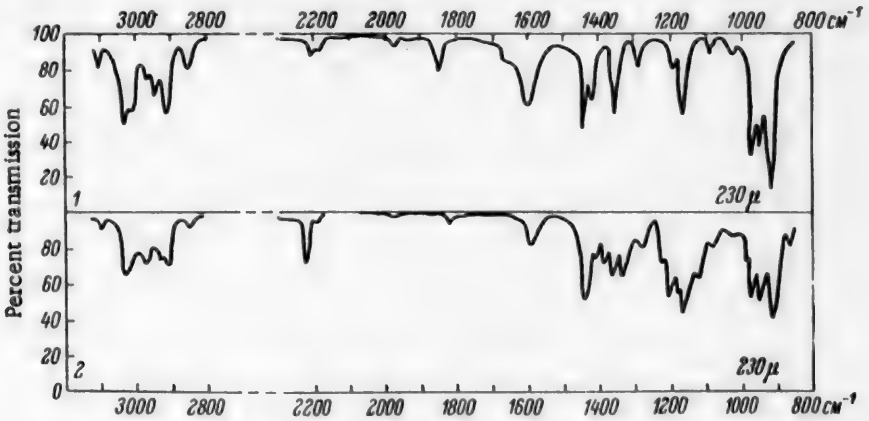


Fig. 2. Infrared transmission spectra. 1) Solution in CCl_4 of 1,5-heptadien-3-yne; 2) solution of the products of bromination of 1,5-heptadien-3-yne with 1 mole bromine in CCl_4, same molar concentration.

The conclusion as to the structure of the main part of the bromoethers was confirmed chemically as follows. The mixture of bromoethers was submitted to the action of alcoholic KOH. The resulting mixture of diene ethers was hydrolyzed by dilute acid to the enyne ketones. The latter were reduced to the saturated ketones. The infrared spectrum of the resulting mixture saturated ketones differed little from the spectrum of methylamyl ketone and differed strongly from the spectrum of ethylbutyl ketone.

We should also observe that in the infrared spectrum of the dienyne ether (Fig. 1, curve 6) there was an intense frequency at 888 cm^{-1} which could be related only to deformation oscillation of the group $CH_2 = C$, which indicates the considerable content of the corresponding ethers (III) and (IV) in the reaction products. Dienyne ethers and enyne ketones were not isolated in pure form.

The addition of lithium alkyls to vinylpropenylacetylene goes exclusively or almost exclusively on the vinyl group with formation as a result of the treatment of the adduct with water of the corresponding propenylalkylallene hydrocarbons (V a and b).

$$(I) \xrightarrow{Li-R} CH_3-CH=CH-CH=C=CH-CH_2-R \qquad (Va \text{ and } b)$$

(Va, $R = C_2H_5$; Vb, $R = C_4H_9$).

In the infrared spectra of hydrocarbons (V a and b) there is practical absence of frequencies of the triple bond and the vinyl group. Deformation frequency of the disubstituted double bond (964 cm^{-1}) is not changed in intensity as compared to the starting hydrocarbon. In the spectra there appear intense frequencies of the disubstituted allene grouping (1955 and 880 cm^{-1}) (Fig. 1, curves 3 and 4). Thus, the resulting hydrocarbons can be assigned only formulas (V a and b).

The structure of the hydrocarbons was confirmed also by a chemical method. When they were exhaustively hydrogenated over $Pd/CaCO_3$ they gave saturated hydrocarbons with only the normal structure. Any other addition not on the vinyl group would lead to formation of hydrocarbons with an iso structure.

The saturated hydrocarbons were identified by constants and by infrared spectra.

Thus, as a result of this investigation it has been established that the direction of addition to vinylpropenylacetylene of alkyl hypobromites is first determined by electron shifts in its molecule, which is not surprising, since this reaction clearly has an ionic mechanism. The order of addition of lithium alkyls does not depend on electron shifts in the dienyne molecule and is determined by spacial conditions: the radical always goes to the least substituted atom of the conjugated system. This rule is obeyed also in other addition reactions of lithium alkyls [5].

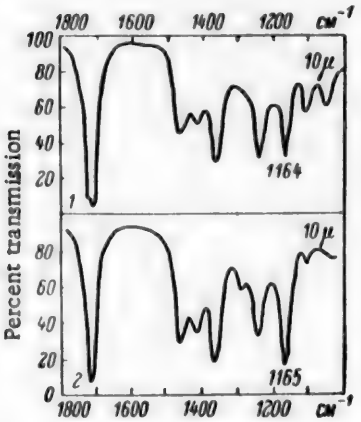


Fig. 3. Infrared transmission spectra. 1) Methylamyl ketone from the product of bromomethylation of 1,5-heptadien-3-yne; 2) pure methylamyl ketone.

From these results it follows that addition of lithium alkyls to multiple bonds is chiefly a homolytic process in which there is participation of the strongly polarized molecule of lithium alkyl or its complex with the solvent [6].

Incidently we carried out orienting experiments to establish the direction of addition to vinylpropenylacetylene of bromine. For this purpose we compared the infrared spectra of solutions of hydrocarbon (I) in CCl_4 with the spectrum of the product of its bromination in the same solvent by one mole of bromine. We found that the deformation frequency of the vinyl group (971 cm^{-1}) was more strongly weakened than the frequency of the group $-CH=CH-$ (951 cm^{-1}). Hence, also in the addition of bromine there is some selectivity (Fig. 2).

EXPERIMENTAL

1-Hepten-3-yne-6-ol (II). Into a solution of sodium amide prepared from 69 g of sodium in 1.5 liters of liquid ammonia we passed gaseous vinylacetylene (190 g of liquid) for six hours, and then by drops we added propylene oxide (180 g). After evaporation of the ammonia the alcohol was extracted from the residue with ether. We obtained 110 g (33.3%) of alcohol (II) (based on vinylacetylene).

B.p. 78.5° (20 mm), d_4^{20} 0.9071, n_D^{20} 1.4885, MR 35.01; calc. 33.58.

Found %: C 76.33, 76.30; H 9.17, 9.30. $C_7H_{10}O$. Calculated %: C 76.32; H 9.15.

Infrared spectrum: 828 s, 883 w, 933 v.s, 971 s, 1010 m, 1060 s, 1081 v. s, 1111 v. s, 1162 s, 1210 s, 1280 s, 1301 s, 1347 s, 1371 s, 1405 s, 1425 s, 1445 s, 1608 s, 1840 m, 1940 v. w, 1283 w, 2226 s, 2725 m, 2837 m, 2903 v. s, 2926 v. s, 2973 v. s, 3013 s, 3047 m, 3102 s, 3347 v. s (wide) cm^{-1}.

1,5-Heptadien-3-yne (vinylpropenylacetylene) (I). By the action of 82.4 g of p-toluenesulfonyl chloride on a solution of 44 g of alcohol (II) in 56 ml of anhydrous pyridine we obtained the tosyl ester. Yield 107 g. The tosyl ester was added dropwise to a boiling 30% KOH solution to which had first been added 3 ml of the Petrov contact agent, and most of the hydrocarbon distilled off as it was formed. The remaining portion was steam distilled. We obtained 30 g (81.5%) of vinylpropenylacetylene (I).

B.p. 54-56° (85 mm), d_4^{20} 0.8029, n_D^{20} 1.5132, MR 34.50; calc. 31.59.

Found %: C 91.32, 91.38; H 8.82, 8.59. C_7H_8. Calculated %: C 91.25; H 8.75.

Infrared spectrum: 702 s, 720 v. s, 745 s, 918 v. s, 951 s, 971 s, 1029 w, 1068 v. w, 1085 w, 1118 w, 1165 m, 1185 m, 1212 v. w, 1290 m, 1365 m, 1398 w, 1415 m, 1440 s, 1586 s, 1603 s, 1620 m, 1662 w, 1732 v. w, 1843 m, 1988 v. w, 2197 m, 2857 m, 2878 w, 2915 s, 2940 m, 2971 m, 3011 s, 3030 s, 3081 w, 3103 m cm^{-1}.

In exhaustive hydrogenation of 2.2 g of 1,5-pentadien-3-yne (I) in 20 ml of methanol over 2 g of $Pd/CaCO_3$ we obtained n-heptane with b.p. 96-98°, d_4^{20} 0.6865, n_D^{20} 1.3890, which agreed with the literature data [7]. The infrared spectrum of the hydrocarbon in the region 800-1600 cm^{-1} was identical with the spectrum of known n-heptane.

Bromoalkoxylation of 1,5-heptadien-3-yne (I). To a solution of 15 g of hydrocarbon (I) in 80 ml of methanol with mechanical stirring and cooling to -5° we added in small portions over six hours 23 g of benzenesulfodibromoamide. The resulting bromoethers were steam distilled and then distilled in a vacuum. We thus obtained the following fractions: 1st, 50-54° at 85 mm, hydrocarbon (I), 3.6 g; 2nd, to 102° (20 mm) 0.2 g; 3rd, 102-110°, 3.7 g; 4th 110-115°, 0.9 g; 5th, 115-125°, 0.9 g; 6th, above 125°, 3.0 g.

For the main fraction of bromoethers we found: b.p. 102-110° (20 mm), d_4^{20} 1.2813, n_D^{20} 1.5158, MR 47.86; calc. 46.08.

Found %: Br 39.01, 38.96. $C_8H_{11}OBr$. Calculated %: Br 39.35.

The infrared spectrum is given in Figure 1 (curve 5).

In the reaction on 6 g of the bromoether of a 10% solution of KOH with heating there was obtained about 2 g of dienyne ether with b.p. 60-64° (10 mm). The infrared spectrum of this mixture is given in Figure 1 (curve 6).

The mixture of dienyne ethers was stirred at 30° for 10 hours with 5% H_2SO_4. The ketones were extracted with ether. The ether extract was washed with a soda solution, dried over Na_2SO_4, and exhaustively hydrogenated over $Pd/CaCO_3$. The infrared spectrum of the resulting mixture of saturated ketones is given in Figure 3 (curve 1). The same figure shows the spectrum of known methylamyl ketone (curve 2).

Addition of lithium ethyl to 1,5-heptadien-3-yne (I). To an ether solution of lithium ethyl obtained from 6 g of lithium was added with stirring and cooling 9 g of heptadienyne (I). The reaction mixture was decomposed with ice water. Vacuum distillation of the mixture gave 5 g (42%) of triene hydrocarbon (Va) and 6 g of higher boiling products.

2,4,5-Nonatriene (Va).

B.p. 62° (20 mm), d_4^{20} 0.7826, n_D^{20} 1.4856, MR 44.80; calc. 42.36.

Found %: C 88.15, 87.81; H 11.66, 11.58. C_9H_{14}. Calculated %: C 88.45; H 11.55.

Infrared spectrum: 694 s, 718 s, 771 m, 805 m, 880 s, 925 s, 964 s, 1088 w, 1066 w, 1111 m(?), 1232 w, 1262 w, 1300 w, 1331 w, 1364 w, 1379 s, 1440 s, 1452 s, 1460 s, 1631 w, 1955 s, 2733 w, 2873 s, 2931 v. s, 2960 v. s, 3017 s cm^{-1}.

On hydrogenation of 1.8 g of the hydrocarbon on colloidal palladium it absorbed 1028 ml of H_2 (20°, 755 mm) which was 94% of the theory. The hydrocarbon was separated by steam distillation and washed with concentrated H_2SO_4.

B.p. 149-151°, d_4^{20} 0.7186, n_D^{20} 1.4055, which agrees with the literature data for n-nonane [7].

Infrared spectrum: 719 s, 751 w, 775 w, 840 w, 891 m, 924 w, 974 w, 991 w, 1042 w, 1083 m, 1137 m, 1189 w, 1216 w, 1255 w, 1301 m, 1341 m, 1379 s, 1452 s, 1471 s cm^{-1} (fully corresponds to the spectrum of n-nonane).

Addition of lithium butyl to 1,5-heptadien-3-yne (I). By the method given above from 9 g of 1,5-heptadien-3-yne was obtained 8 g of triene hydrocarbon (55%) and 4 g of higher boiling residue.

2,4,5-Undecatriene (Vb).

B.p. 95-96° (20 mm), d_4^{20} 0.7912, n_D^{20} 1.4818, MR 54.12; calc. 51.60.

Found %: C 87.83, 87.78; H 12.34, 12.32. $C_{11}H_{18}$. Calculated %: C 87.92; H 12.08.

Infrared spectrum: 693 s, 719 s, 770 m, 805 m, 832 w, 876 s, 897 w, 925 m, 965 v. s, 1025 v. w, 1109 w(?), 1140 v. w, 1229 w, 1271 w, 1300 w, 1332 v. w, 1362 w, 1379 s, 1400 v. w, 1440 s, 1454 s, 1463 s, 1619-1632 w, 1951 s, 2731 w, 2857 s, 2871 s, 2927 v. s, 2958 s, 3017 s, 3024 s cm^{-1}.

On hydrogenation of 2.1 g of hydrocarbon on colloidal palladium it absorbed 1020 ml of H_2 (21°, 748 mm) which was 97.1% of the theory. The hydrocarbon was steam distilled and washed with concentrated H_2SO_4.

B.p. 194.5-195.5°, d_4^{20} 0.7408, n_D^{20} 1.4172, which agrees with the literature data for n-undecane [7]. The infrared spectrum of the substance agreed with the spectrum of known n-undecane.

SUMMARY

1. Splitting of the tosyl ester of 1-hepten-3-yne-6-ol gives 1,5-heptadien-3-yne (vinylpropenylacetylene).

2. We have shown that under the action of benzenesulfodibromoamide on an alcoholic solution of vinylpropenylacetylene the addition of methyl hypobromite occurs preferentially on the vinyl group.

3. We have established that the same hydrocarbon adds lithium alkyls (lithium ethyl and lithium butyl) exclusively or almost exclusively on the vinyl group with formation of propenylalkylallenes.

4. We have suggested that addition of lithium alkyls to dienyne hydrocarbons has a homolytic character and its direction is determined first by steric factors.

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STUDIES IN THE FIELD OF THE CHEMISTRY OF ORGANIC OXIDES

XIX. THE REACTION OF α-OXIDES OF CHLOROPRENE WITH AMMONIA AND AMINES

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The addition of ammonia and amines to organic α-oxides goes according to the well known rule of A. K. Krasuskii [1]. According to his mechanism, this reaction is a nucleophilic substitution (or addition) in which the ammonia and amine attack preferably the most spacially accesible and least electronegative carbon atom of the oxide ring [2].

In the case of conjugated ethylene oxides this rule is observed, but the possibility of stabilization of the positive charge in opening the oxide ring (because of conjugation with the double bond) on the α-carbon atom with respect to the double bond permits formation of some quantity of other possible isomers.

In the literature there is described the addition of ammonia and amines to oxides of divinyl [3, 4], isoprene [5, 6], and piperylene [7].

There is the greatest interest in this work for a study of the addition of ammonia and amines to oxides of isoprene. Due to the great difference in boiling point of the isomeric addition products in this case, they were isolated and the amino alcohols formed in accord with the rule of A. K. Krasuskii composed about 90% of the mixture of isomers.

In the present work we consider the reaction of chloroprene oxide with ammonia and amines.

It is known from the literature that on catalytic hydrogenation of chloroprene oxide there is formed a mixture of 3-chloro-3-buten-1-ol, and 3-chloro-2-buten-1-ol (1,4 addition) [8]; on hydration it forms 3-chloro-3-buten-1,2-diol [9]; it adds hydrogen halides with formation of primary alcohols preferentially [9]; with alcohols in the presence of an alkaline catalyst it forms 65% of the primary glycol ether and in the presence of acid catalysts, only the secondary one [10, 11].

A peculiarity of chloroprene oxide is the presence in the α-position of a chlorine atom. In a series of saturated oxides such a halogen next to the oxide bond leads to preferential formation of adducts with a "meso" position of the hydroxyl group, independent of the acid-base nature of the catalyst or reagents [12, 13].

In combination with the presence of unsaturation, the halogen atom can cause another effect also, as, for example, occurs in hydrogenation of chloroprene oxide: conjugation of the chlorine atom with a double bond partly withdraws it from conjugation with the oxide ring so that 1,4 addition of hydrogen occurs to less extent than, for example, in the case of divinyl oxide [8].

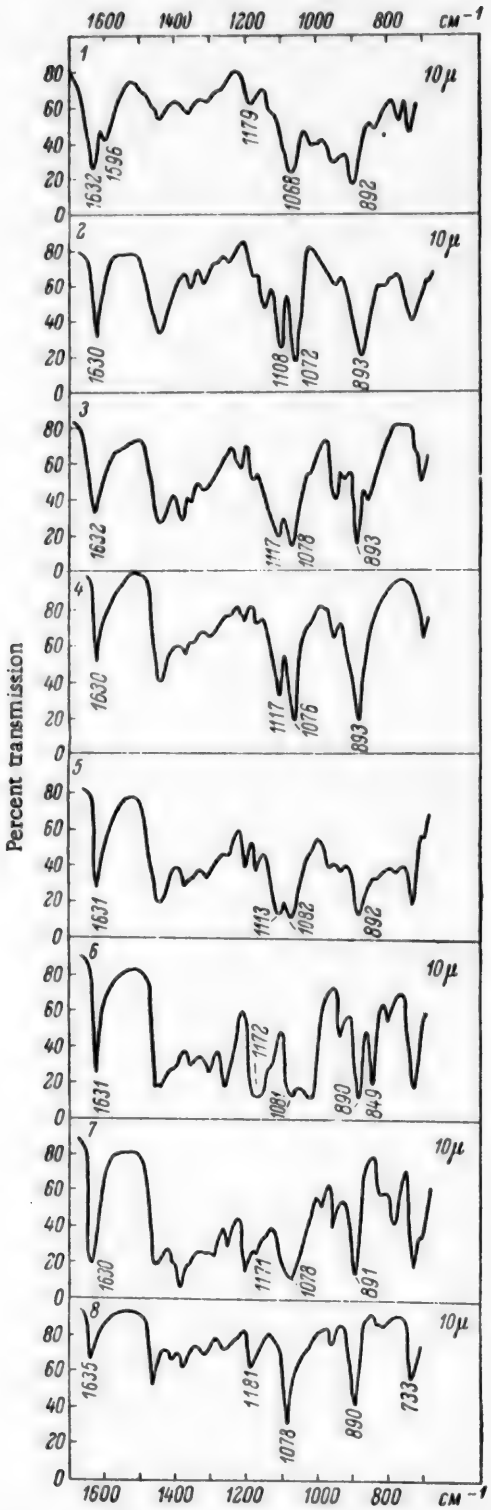
As a result of addition to chloroprene oxide of ammonia, four primary, and three secondary amines we obtained eight primary, secondary, and tertiary amino alcohols, whose formulas and constant are given in Table 1.

From the data of Table 1 it is evident that the boiling points of the secondary amino alcohols are higher than those of the isomeric tertiary ones, as has been observed in other analogous series [3, 4]. The specific gravities and indexes of refraction in homologous series of secondary and tertiary amino alcohols are lowered. The refractive indexes in secondary amino alcohols are higher than in tertiary ones.

Primary and secondary amino alcohols crystallize several days after distillation. Tertiary amino alcohols remain in the form of viscous oils.

All these amino alcohols form picrolonates which crystallize well from alcohol solution.

As a result of addition to chloroprene oxide of ammonia and amines we could expect formation in each case of two isomeric alcohols. Conjugated addition of ammonia and amines with formation of hydroxyamines of type (III) never occurs, as the literature shows.



$$CH_2{=}CCl{-}CHOH{-}CH_2NR_2$$
(I)

$$CH_2{=}CCl{-}CHNR_2{-}CH_2OH$$
(II)

$$CH_2NR_2{-}CCl{=}CH{-}CH_2OH$$
(III)

As a result of distillation of the reaction products we isolated in all cases practically individual substances. Attempts to fractionate the picrolonates obtained from them did not succeed: all the picrolonate fractions had the same properties.

The structure of the resulting amino alcohols was chiefly shown by their infrared spectra (Fig. curves 1-8). In all cases the double bond gave a frequency of about 1630 cm^{-1} and deformation oscillation in the group $CH_2 = C$ a frequency of about 890 cm^{-1}. Valence oscillation of the secondary hydroxyl group in the α-position to the double bond gave in the spectra intense bands at 1070-1080 cm^{-1}. Oscillation at the bond C−N evidently corresponded to a frequency of about 1117 cm^{-1} in the case of the secondary amines and about 1170-1180 cm^{-1} in the case of the tertiary amines. In the infrared spectrum of the primary amino alcohol there is an intense deformation frequency of the primary amino group at 1596 cm^{-1}.

All these results correspond to formula (I). Primary alcohols of type (II) have in the infrared spectra an intense frequency of valence oscillation of the hydroxyl group at 1020-1040 cm^{-1} [14]. In the spectra of our amino alcohols in this region there is either no absorption at all, or a very weak undifferentiated frequency. Only in the case of the adduct of dimethylamine (R = CH_3) is there an intense band in this region, the origin of which is rather different.

Infrared transmission spectra. 1) 1-Amino-3-chloro-3-buten-2-ol; 2) 1-methylamino-3-chloro-3-buten-2-ol; 3) 1-ethylamino-3-chloro-3-buten-2-ol (5% solution in CCl_4); 4) 1-propylamino-3-chloro-3-buten-2-ol (5% solution in CCl_4); 5) 1-butylamino-3-chloro-3-buten-2-ol; 6) 1-dimethylamino-3-chloro-3-buten-2-ol; 7) 1-diethylamino-3-chloro-3-buten-2-ol; 8) 1-dibutyl-amino-3-chloro-3-buten-2-ol.

TABLE 1. Constants of Amino Alcohols

Substance	M. p.	B. p. (20 mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	Yield, %	M. p. of picrolonate
$CH_2=CCl-CHOH-CH_2NH_2$	40—42°	110.5—111°	1.2101	1.5032	29.70	30.02	41	236°
$CH_2=CCl-CHOH-CH_2NHCH_3$	38—39	101.5—102	1.1286	1.4859	34.49	34.82	43	181—182
$CH_2=CCl-CHOH-CH_2NHC_2H_5$	36—37	110—111	1.0863	1.4810	39.20	39.43	47	193.5—194.5
$CH_2=CCl-CHOH-CH_2NHC_3H_7$	37—38	116—116.5	1.0582	1.4772	43.71	44.05	63	175—175.5
$CH_2=CCl-CHOH-CH_2NHC_4H_9$	28—29	128—129	1.0369	1.4759	48.32	48.67	62	167.5
$CH_2=CCl-CHOH-CH_2N(CH_3)_2$	—	79.5—80.5	1.0592	1.4705	39.45	39.77	70	182.5—183
$CH_2=CCl-CHOH-CH_2N(C_2H_5)_2$	—	98—99	1.0007	1.4638	48.98	49.01	75	137
$CH_2=CCl-CHOH-CH_2N(C_4H_9)_2$	—	145.5—146.5	0.9577	1.4618	67.08	67.48	79	121.5—122

TABLE 2. Analytical Data for Amino Alcohols

$CH_2=CCl-CHOH-CH_2NR'R''$		Empirical formula	Found (%)				Calculated (%)				Picrolonates: content of N (%)	
R'	R''		C	H	N	Cl	C	H	N	Cl	found	calc.
H	H	C_4H_8ONCl	40.02, 40.09	6.97, 6.77	11.42, 11.72	29.29, 29.41	39.52	6.33	11.52	29.17	18.14, 18.36	18.16
H	CH_3	$C_5H_{10}ONCl$	44.26, 43.98	7.49, 7.65	9.97, 9.95	26.15, 25.89	44.29	7.44	10.33	26.15	17.87, 18.00	17.52
H	C_2H_5	$C_6H_{12}ONCl$	48.51, 48.56	8.19, 8.26	9.44, 9.43	23.41, 23.25	48.16	8.08	9.36	23.70	16.73, 17.05	16.95
H	C_3H_7	$C_7H_{14}ONCl$	51.57, 51.69	8.59, 8.73	8.51, 8.34	21.46, 21.46	51.13	8.62	8.56	21.67	16.25, 15.98	16.37
H	C_4H_9	$C_8H_{16}ONCl$	54.23, 54.47	9.24, 9.23	7.91, 8.21	19.88, 19.92	54.08	9.08	7.88	19.95	15.58, 15.41	15.85
CH_3	CH_3	$C_6H_{12}ONCl$	48.02, 47.87	8.11, 8.32	9.26, 9.13	23.51, 23.76	48.16	8.08	9.36	23.70	16.98, 17.22	16.95
C_2H_5	C_2H_5	$C_8H_{16}ONCl$	55.24, 55.27	9.20, 9.32	7.86, 7.38	20.03, 19.75	54.08	9.08	7.88	19.95	15.26, 15.77	15.85
C_4H_9	C_4H_9	$C_{12}H_{24}ONCl$	61.53, 61.39	10.34, 10.35	5.80, 5.73	15.23, 15.69	61.65	10.35	5.99	15.17	14.29, 14.27	14.36

The strucutre of one amino alcohol, 1-amino-3-chloro-3-buten-2-ol, was also shown by a chemical method. Its hydrogenation on palladium gave the known 1-amino-2-butanol which forms an oxalate with m.p. 193° [15].

Thus we have established that in distinction from isoprene oxide, chloroprene oxide adds amines exclusively or almost exclusively according to the Krasuskii rule with formation of amino alcohols with secondary alcohol groups. Such an addition is certainly due to the presence of atom of chlorine in the α-position to the oxide bond; the occurrence of a positive charge on the carbon atoms when the oxide ring is opened is a disadvantage (vicinal effect).

EXPERIMENTAL

Chloroprene oxide was obtained from chloroprene through the bromohydrin [9]. Its reaction with ammonia and amines was carried out under analogous conditions.

To 4-5 fold excess of a 33-40% water solution of amine with stirring and cooling was added dropwise chloroprene oxide (10-15 g). After stirring for several hours the mixture was allowed to stand for a day. The reaction product was salted out along with the amine by dry potash and dried over the same substance. Ammonia and volatile starting amines were distilled off by heating on a water bath. In the case of difficultly volatile amines, all the distillation was carried out in a vacuum.

In Table 2 we give analyses of the resulting amino alcohols and their picrolonates.

1-Amino-3-chloro-3-buten-2-ol (3 g) was hydrogenated in 25 ml of methanol over 2 g of $Pd/CaCO_3$ (palladium content 1.2%). After 50 minutes it absorbed the calculated amount of hydrogen, after which hydrogenation was stopped. After separation of the catalyst from the reaction mixture, the methyl alcohols was distilled off and the resulting 1-amino-2-butanol was vacuum distilled. Yield 85%. B.p. 75.5-76° (12 mm), d_4^{20} 0.9777, n_D^{20} 1.4475.

A solution of 0.37 g of this amino alcohol in 5 ml of anhydrous ethanol was mixed with a solution of 0.33 g of oxalic acid in 5 ml of the same solvent. The mixture was heated to boiling and then allowed to stand for a day. The oxalate, washed with alcohol, melted at 191°. After recrystallization from aqueous alcohol, m.p. 193°, which agreed with the literature value for 1-amino-2-butanol oxalate.

The infrared spectra of the amino alcohols were taken on a IKS-14 spectrophotometer with a NaCl prism.

SUMMARY

1. We have studied the reaction of addition of ammonia and primary and secondary amines to chloroprene oxide.

2. We have showed that the addition goes exclusively or almost exclusively in accord with the Krasuskii rule with formation of amino alcohols with secondary hydroxyl groups.

3. For all of the amino alcohols which were isolated we have obtained crystalline picrolonates.

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SYNTHESIS OF DERIVATIVES OF DIHYDROFURAN

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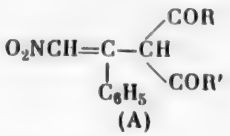
The interaction of β-halo-substituted arylnitroalkenes, in particular β-bromo-β-nitrostyrene, with substances containing active methylene groups has not been systematically investigated. Dehydrohalogenation of the products of condensation could be of interest in providing a route to synthesis of diverse derivatives of unsaturated nitro compounds.

β-Halo-β-nitroalkenes and α-aryl-β-halo-β-nitroalkenes are also interesting because of the possibility of transformation by dehydrohalogenation into nitroalkynes which have scarcely been studied [1, 2].

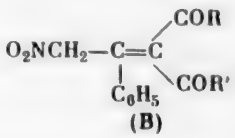
With malonic ester in presence of sodium methoxide, β-bromo-β-nitrostyrene formed the usual product of the Michael condensation (I), which on heating with an equimolar quantity of triethylamine split off hydrogen bromide.

Other β-dicarbonyl compounds (ethyl acetoacetate, acetylacetone, benzoylacetone, dimedon) at once give triethylamine hydrobromide on reaction with β-bromo-β-nitrostyrene in presence of triethylamine.

Judging by the analytical data, each of the synthesized compounds could have structure A or B.



(A)

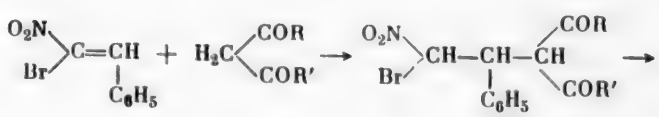


(B)

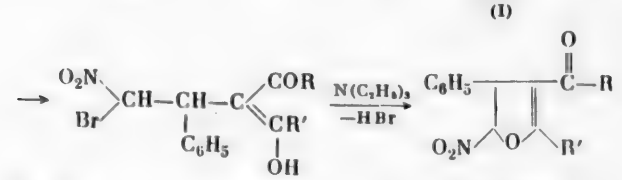
Products of structure (A) can be formed by addition of the methylene component to β-bromo-β-nitrostyrene and subsequent dehydrohalogenation; compounds of type (B) can be formed by isomerization of (A).

These assumptions about the structure of the compounds were put in doubt, however, by investigation of the products: a double bond was not detected by bromination; hydrolysis did not convert them respectively into benzoylacetic and phenylfumaric acid; the product of condensation of β-bromo-β-nitrostyrene with acetylacetone formed only a mono-p-nitrophenylhydrazone (VII).

In the light of these observations the following mechanism, leading to formation of dihydrofuran derivatives (II)-(VI), was proposed:



(I)



(II–VI)

(I), (II) R = R′ = OCH_3;
(III) R = OC_2H_5, R′ = CH_3;
(IV) R = R′ = CH_3;
(V) R = CH_3, R′ = C_6H_5;
(VI) R, R′ = $CH_3C(CH_3)_2CH_3$.

TABLE 1

Substance	Intensities*		
	$-C_6H_5$	$-C=C-$	$-NO_2$
$C_6H_5-CH=C-NO_2$	2.4	4.3	9
$C_6H_5CH=CH-COOR$	0.7+1.0	1+2	—
$CH_2=CH-COOH$	—	0.04	—
CH_3NO_2	—	—	0.02
$C_6H_5CH_3$	0.02	—	—
(II)	—	0.1	<0.01+0.02
(III)	0.035	0.08+0.15	<0.01+0.02
(IV)	0.01+0.02	0.1+0.2	0.01+0.02
(V)	1.0	0.5+1.0	<0.01+0.02
(VI)	0.06	0.15+0.30	<0.01+0.02

* In a single arbitrary scale.

TABLE 2. Constants and Analytical Data of Compounds (III) - (VI)

Compound	Melting point	Found %			Empirical formula	Calculated %			Molecular weight		Yield (in %)
		C	H	N		C	H	N	found	calculated	
(III)	75°	60.97, 60.53	5.92, 5.80	5.11, 5.25	$C_{14}H_{15}O_5N$	60.62	5.45	5.05	265, 282	277.1	70
(IV)	95	62.97, 63.15	5.66, 5.94	5.76, 5.85	$C_{13}H_{13}O_4N$	63.12	5.30	5.66	255, 240	247.1	67.2
(V)	142	69.91, 69.99	5.38, 5.26	4.53, 4.50	$C_{18}H_{15}O_4N$	69.87	4.89	4.53	320, 331	309.1	30
(VI)	108	66.75, 66.90	6.17, 6.33	5.06, 5.03	$C_{16}H_{18}O_4N$	66.63	6.29	4.86	295, 303	288.2	80.6

Another possibility in this connection was isomerization of the double bond in the 3-4 position of the dihydrofuran ring [3].

The problem of the structure of the compounds could be satisfactorily solved by examination of the intensities of the Raman bands of compounds (II) - (VI).

If these compounds had structure (A), they should contain the conjugated nitrostyrene system; if they had structure (B) they should contain either the cinnamic acid grouping or a benzylidene ketone grouping and an unconjugated nitro group. Dihydrofuran derivatives (II)-(VI) should contain the grouping of acrylic acid or a vinyl ketone and an unconjugated benzene ring and a nitro group.

We had earlier established that the intensity coefficients of the bands of the Raman spectra for vibrations of the benzene ring, the double bond, and the nitro group all vary by several orders of magnitude in dependence on the nature of their conjugation [4, 5]. It was therefore appropriate to make use of the intensity coefficients of the bands for the respective vibrations in the assignment of structures to the compounds of interest to us.

Nitro group, benzene ring, and double-bond frequencies were found in the spectra of compounds (II)-(IV); their intensities coincided with (or were close to) those of the unconjugated nitro group, the benzene ring, and the double bond conjugated with a carboxyl (or carbonyl) group. These structural components are precisely those present in compounds (II)-(IV) (Table 1). Consequently, there could be no doubt about the dihydrofuran structure of the products of interaction of β-bromo-β-nitrostyrene with the active methylenic substances in question.

The higher intensities of the benzene ring and double-bond bands in substance (V), which are close to the corresponding values in cinnamic acid, suggest that (V) was formed by enolization of the carbonyl group adjacent to the benzene ring and not of the one adjacent to the methyl group. The intensities of the double-bond bands in compounds (II)-(VI) are slightly higher than those of acrylic acid, evidently due to conjugation of this bond with the unshared electron pair of the oxygen of the furan ring.

EXPERIMENTAL

Methyl ester of α-carbomethoxy-β-phenyl-γ-bromo-γ-nitrobutyric acid (I). At 0-5° a cold solution of 13.6 g of bromonitrostyrene in 300 ml of methanol was added to a solution of 7.9 g of dimethyl malonate in 10 ml of methanol and 1.32 g of metallic sodium. The mixture was held at 0-5° for 1.5 hr and then neutralized with 20% acetic acid. The white crystals were separated on a filter and washed with cold water. M.p. 96° (from ethanol). Yield 13 g (78.3%).

Found %: C 43.62, 43.46; H 3.97, 4.11; N 4.20, 3.92. $C_{13}H_{14}O_6NBr$. Calculated %: C 43.31; H 3.91; N 3.88.

Condensation of bromonitrostyrene with ethyl acetoacetate under similar conditions at once yielded the cyclization product (III).

2-Methoxy-3-carbomethoxy-4-phenyl-5-nitro-4,5-dihydrofuran (II). A solution of 9.3 g of (I) in 60 ml of anhydrous benzene and 3 ml of triethylamine were boiled for 10 hr. The hydrobromide of triethylamine (3.5 g, 80%) came down and was collected on a filter. A yellow-brown oil remained behind (6.6 g, 90%) after removal of the benzene in the vacuum of a water jet pump. The oil was fractionally distilled in vacuo to give a yellow, viscous liquid with b.p. 142-152° (0.6 mm); yield 3.0 g (41%).

Found %: C 56.17, 56.10; H 4.56, 4.74; N 4.79, 4.56. $C_{13}H_{13}O_6N$. Calculated %: C 55.89; H 4.65; N 5.01.

2-Methyl-3-carboethoxy-4-phenyl-5-nitro-4,5-dihydrofuran (III). A solution of 16.6 g of bromonitrostyrene in 50 ml of anhydrous benzene, 15 ml of ethyl acetoacetate, and 10.2 ml (1.5% excess) of triethylamine were boiled for 5 hr. Triethylamine hydrobromide gradually separated; after the mixture had cooled, the hydrobromide was collected on a filter and washed with 10 ml of ether. Yield 13.2 g (quantitative). After the solvent had been evaporated (at room temperature), crystals came down and were separated from minor amounts of resin on a porous plate. Compound (III) formed stout, white crystals. M.p. 75° (from ethanol). Yield 14 g (70%).

Compounds (IV)-(VI) were synthesized in similar fashion.

p-Nitrophenylhydrazone of 2-methyl-3-acetyl-4-phenyl-5-nitro-4,5-dihydrofuran (VII). A solution of 0.5 g of 2-methyl-3-acetyl-4-phenyl-5-nitro-4,5-dihydrofuran (IV) in 5 ml of ethanol and 0.3 g of p-nitrophenylhydrazine in 5 ml of ethanol were boiled for 3 min, three drops of glacial acetic acid were added, and the mass was held at 18° for 12 hr; a golden precipitate appeared. M.p. 160° (from ethanol). Yield 0.5 g (72.4%).

Found %: C 59.80, 59.75; H 4.82, 4.86; N 14.87, 14.63. $C_{19}H_{18}O_5N_4$. Calculated %: C 59.66; H 4.74; N 14.65.

SUMMARY

1. A method of synthesis of dihydrofuran derivatives is proposed.

2. Data for intensities of the Raman spectra enabled establishment of the structure of products of reaction of β-bromo-β-nitrostyrene with substances containing active methylene groupings.

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INTERACTION OF ETHYL ACETOACETATE WITH β-NITROSTYRENES

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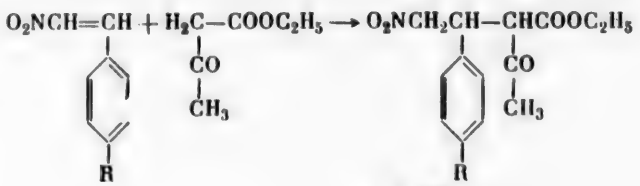
The reaction of unsaturated nitro compounds with ethyl acetoacetate has attracted the attention of investigators because of its versatility for synthesis by simple routes of compounds of practical importance (γ-nitroketo acids, γ-aminoketo acids, γ-aminoketones, furan derivatives).

Ethyl acetoacetate has been reacted in presence of alcoholic sodium ethoxide with 1-nitropropylene-1 [1], 2-nitro-4-methylpentene-2 [2], β-nitro-β-methylstyrene and β-nitro-β-ethylstyrene [3], as well as with some cyclic nitroolefins [4]. For the first time we effected the reaction of β-nitrostyrene with ethyl acetoacetate in presence of triethylamine and pyridine as catalysts in a benzene medium [5, 6]. The reaction led to high yields (98 and 82% repsectively) of the ethyl ester of α-acetyl-β-phenyl-γ-nitrobutyric acid.

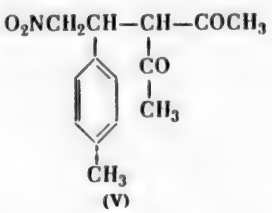
It was of interest to establish the relation between structure of unsaturated nitro compounds and their ability to condense with ethyl acetoacetate in presence of organic bases. With this objective various para-substituted β-nitrostyrenes were brought into reaction. Addition took place in accordance with our previously established [5, 6] general scheme.



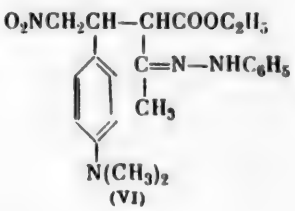
(I–IV)
(I) R = NO₂,
(II) R = CH₃,
(III) R = OCH₃,
(IV) R = N(CH₃)₂.

Acetylacetone formed addition product (V) with α-(p-tolyl)-β-nitroethylene.

The presence of a carbonyl group in the condensation products was confirmed by transformation of one of them (IV) into the corresponding phenylhydrazone (VI).



(V)



(VI)

EXPERIMENTAL

Ethyl ester of α-acetyl-β-(p-tolyl)-γ-nitrobutyric acid (II). To a solution of 0.64 g of α-(p-tolyl)-β-nitroethylene in 15 ml of anhydrous benzene and 1 g of ethyl acetoacetate were added six drops of triethylamine.

TABLE 1. Conditions of Reaction, Melting Points of Compounds

Addition products	Melting point	Reaction conditions				Yield(%)
		solvent	catalyst	temperature	duration (hr)	
(I)	107°	Benzene	Triethylamine, pyridine	25°	12[a]	64,66
(II)	75	Benzene	Triethylamine	25	48	80
(III)	68	Benzene	Triethylamine	25	336[b]	99
(IV)	102	Acetone	Piperidine	25	12[a]	52
		Acetone	Rodionov catalyst	25	168[c]	57
(V)	104	Benzene	Triethylamine	25	48	49

Note: [a]Mixture boiled 30 min until the nitroalkene had fully dissolved, and then held for 12 hr at 25°.
[b]After 336 hr at 25° and evaporation of solvent at room temperature, the condensation product was isolated after five days.
[c]The resinous product was treated with a little ethanol and suction-dried on a a porous tile.
[d]Condensation product was isolated when not more than 0.002 mole nitroalkene was brought into reaction.

TABLE 2. Analytical Data for Compounds (I)-(V)

Compound	Found %			Empirical formula	Calculated %			M	
	C	H	N		C	H	N	found	calculated
(I)	52.12, 52.41	5.08, 5.28	8.90, 8.93	$C_{14}H_{16}O_7N_2$	51.82	4.97	8.64	312, 336	324.1
(II)	61.19, 61.38	6.62, 6.62	4.78, 4.92	$C_{15}H_{19}O_5N$	61.39	6.53	4.77	284, 305	293.2
(III)	58.40, 58.52	6.32, 6.41	4.77, 4.72	$C_{15}H_{19}O_6N$	58.22	6.13	4.53	295, 287	309.2
(IV)	59.54, 59.64	7.20, 7.14	8.72, 8.77	$C_{16}H_{22}O_5N_2$	59.59	6.88	8.69	312, 330	322.2
(V)	63.68, 63.76	6.80, 6.72	5.62, 5.52	$C_{14}H_{17}O_4N$	63.84	6.51	5.32	240, 254	263.1

The mixture was held for 48 hr without contact with moisture at 25°. After the solvent had evaporated (at room temperature), the ethyl ester of α-acetyl-β-(p-tolyl)-γ-nitrobutyric acid was isolated.

Under identical conditions α-(p-tolyl)-β-nitroethylene reacted with acetylacetone with formation of 1-nitro-2-(p-tolyl)-3-acetylpentanone-4 (V).

The same procedure was followed for synthesis of ethyl α-acetyl-β-(p-nitrophenyl)-γ-nitrobutyrate (I), ethyl α-acetyl-β-(p-methoxyphenyl)-γ-nitrobutyrate (III), and ethyl α-acetyl-β-(p-dimethylaminophenyl)-γ-nitrobutyrate (IV).

Phenylhydrazone of ethyl α-acetyl-β-(p-dimethylaminophenyl)-γ-nitrobutyrate (VI). To a boiling solution of 0.32 g of compound (IV) in 15 ml of alcohol was added 0.15 g of phenylhydrazine. The mass was held for 48 hr at 20° and the resinous precipitate was drained on a porous plate. Yield 0.15 g (40%). Phenylhydrazone (VI) consisted of fine, yellow crystals with m.p. 144° (from ethanol).

Found %: C 62.33, 62.28; H 7.40, 7.31; N 13.60, 13.75. $C_{22}H_{28}O_4N_4$. Calculated %: C 62.20; H 7.19; N 13.51.

SUMMARY

1. p-Nitro-, p-methyl-, p-methoxyphenylnitroalkenes formed products of condensation with ethyl acetoacetate in presence of triethylamine as catalyst.

2. p-Dimethylaminophenylnitroethylene condensed with ethyl acetoacetate only in presence of piperidine or Rodionov catalyst.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

THE FRIES REARRANGEMENT IN THE 2,6-DINITRO-HYDROQUINONE SERIES

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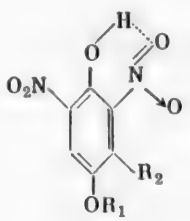
Rearrangement of phenolic ester to p- or o-hydroxyketones (the Fries rearrangement) is regarded as an electrophilic substitution reaction, and the presence in the benzene ring of a substituent (a second order orientant), such as a nitro group, greatly inhibits the reaction. It was therefore not until 1946 that the Fries rearrangement of mononitro derivatives of phenolic esters was realized [1], although attempts had been made very much earlier [2]. The literature is entirely lacking in examples of migration of an acyl group in dinitro derivatives of phenolic esters.

In the course of work on the synthesis of substituted 1,2,3,5-tetrahydroxybenzenes from hydroquinone, we studied the possibility of Fries rearrangement of dinitro compounds, starting from the monoacetate of 2,6-dinitrohydroquinone (I) [3] whose rearrangement should lead to 2,4-dinitro-3,6-dihydroxyacetophenone (II).

Heating of compound (I) with excess of aluminum chloride in nitrobenzene gave the corresponding acetophenone (II), treatment of which with dimethyl sulfate gave 2,4-dinitro-3-hydroxy-6-methoxyacetophenone (III). The empirical analysis of the latter and the melting point of (II) (133-134°) [compared with a melting point of 94-95° for compound (I)] showed the Fries rearrangement also takes place with dinitro derivatives of acylated phenols. This was confirmed by the infrared spectra of compounds (II) and (III) in which the absorption band in the 1650 cm^{-1} region is associated with the carbonyl group (Fig. 1). The infrared spectra of compounds (I), (II), and (III), also the spectrum of 1-hydroxy-4-methoxy-2,6-dinitrobenzene (IV) which was synthesized during the investigation [4], indicated the possible presence of a chelate structure. Intramolecular interaction can occur in this case through closure of the unconjugated six-membered ring.



(I) $R_1 = COCH_3$; $R_2 = H$
(II) $R_1 = H$; $R_2 = COCH_3$
(III) $R_1 = CH_3$; $R_2 = COCH_3$
(IV) $R_1 = CH_3$; $R_2 = H$.

The infrared spectra of the compounds in question contain two absorption bands in the 3100 and 3380 cm^{-1} region [3250 cm^{-1} in the case of (I)]. The first band indicates the presence of an intramolecularly associated hydroxyl group; the second is the consequence of intermolecular association of the hydroxy group. Since an intramolecular hydrogen bond differs from an intermolecular bond in not being broken in a solvent unable to participate in the formation of hydrogen bonds, the 3100 cm^{-1} absorption band is retained in the spectrum of compound (I) plotted in chloroform, whereas the second band nearly disappears. The results are in harmony with the theory that intramolecular association of the OH group leads to shifting towards longer wavelengths of the absorption band characterizing it in the infrared region. The shift is about 500 cm^{-1} for compound (I). An interesting change of color of these compounds is observed. Compound (I) is yellow after recrystallization from alcohol; its alkaline solution acquires a violet color; after chromatography with alumina in a column, the substance becomes red. The

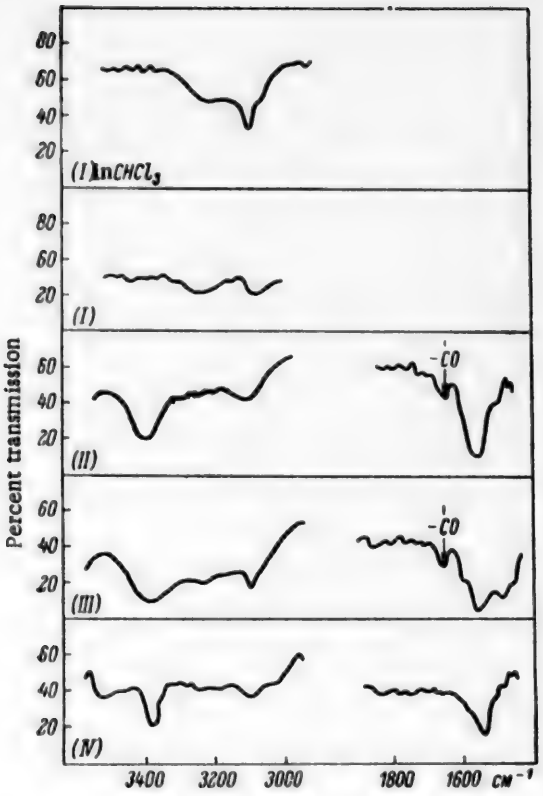


Fig. 1. Infrared absorption spectra (KBr). Details in text.

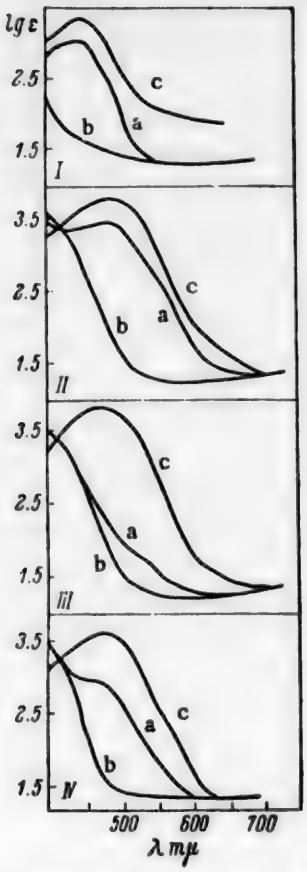


Fig. 2. Absorption spectra in the visible region in alcohol. a) In a neutral medium; b) in absence of hydrochloric acid; c) in presence of sodium hydroxide. Details in text.

absorption spectra of these compounds in the visible region undergo characteristic changes with changing pH of the solution (Fig. 2). These color changes might also be associated with the presence of an intramolecular hydrogen bond. This bond is so stable that attempts to prepare, from compound (I), the dimethyl ether of 2,6-dinitrohydroquinone with the help of dimethyl sulfate were unsuccessful.

EXPERIMENTAL

2,4-Dinitro-3,6-dihydroxyacetophenone (II). A solution of 10 g of 2,6-dinitrohydroquinone 4-monoacetate (m.p. 94-94.5°) in 100 ml of nitrobenzene was slowly added through a dropping funnel to a solution of 25 g of aluminum chloride in 30 ml of nitrobenzene. The mixture was heated for 2 hr on a boiling water bath. After 24 hr the reaction mass was poured into a mixture of 200 g of crushed ice and 50 ml of concentrated hydrochloric acid, and distilled with steam for removal of nitrobenzene. The residue was extracted with ether (5 portions of 50 ml each). After drying with sodium sulfate, the solvent was removed. The residue consisted of yellow crystals. Yield 6.1 g (61%). M.p. 133-134° (from alcohol).

Found %: C 39.47; H 2.58; N 11.88. $C_8H_6O_7N_2$. Calculated %: C 39.68; H 2.50; N 11.57.

2,4-Dinitro-3-hydroxy-6-methoxyacetophenone (III). A solution of 1 g of 2,4-dinitro-3,6-dihydroxyacetophenone in 100 ml of water was prepared by heating to 50°. Addition was then made of 3.2 ml of 20% sodium hydroxide solution (to give a pH of 9-10), after which 1.2 ml of distilled dimethyl sulfate was stirred in dropwise in the course of an hour at 60-65°. The reaction mass was allowed to stand overnight. The precipitate was filtered

off and recrystallized from alcohol. 2,4-Dinitro-3-hydroxy-6-methoxyacetophenone form bright-yellow crystals. Yield 0.56 g (53%). M.p. 94-96°.

Found %: C 41.96; H 3.04; N 11.19. $C_9H_8O_7N_2$. Calculated %: C 42.12; H 3.14; N 10.94.

SUMMARY

It was shown that dinitro derivatives of phenolic esters are able to undergo the Fries rearrangement. 2,4-Dinitro-3,6-dihydroxyacetophenone was obtained from 2,6-dinitrohydroquinone 4-monoacetate. The infrared spectra of a series of dinitrohydrohydroquinone derivatives were examined, and the presence of an intramolecular hydrogen bond in the compounds was confirmed.

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INVESTIGATIONS ON LIPIDES

VI. SYNTHESIS OF TRIGLYCERIDES OF VEGETABLE OILS*

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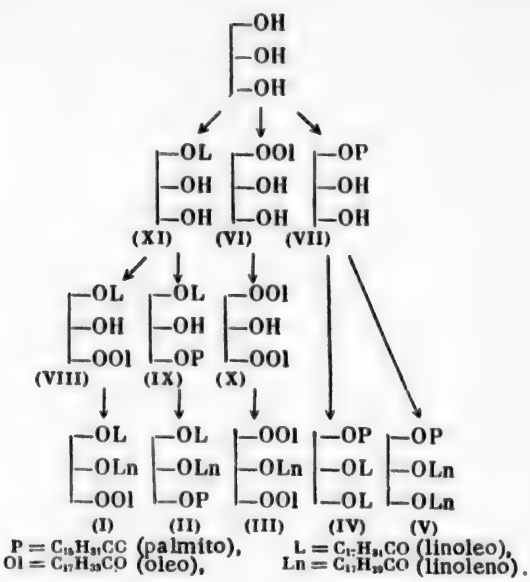
The latest development in investigations on the synthesis of the glyceridic components of linseed [2], soya [3], safflower [4], and other vegetable oils is the preparation of α-linoleo-β-linoleno-α'-olein (I), α-linoleo-β-linoleno-α'-palmitin (II), α,α'-dioleo-β-linolenin (III), α-palmito-α',β-dilinolenin (V).



The mixed triglycerides (I) and (II) were synthesized from α-monolinoleoglycerol (XI) via respectively α-linoleo-α'-oleoglycerol (VIII) and α-linoleo-α'-palmitoglycerol (IX), which were subjected to the action of linolenyl chloride. Triglyceride (III) was similarly prepared by reaction of α,α'-dioleoglycerol [5] (X) with linolenyl chloride. Synthesis of (IV) [6] and (V) was effected by direct introduction of the residues of linolic and linolenic acid into α-palmitoglycerol (VII).

EXPERIMENTAL

α-Linoleo-β-linoleno-α'-olein (I). To a solution of 16 g of α-linoleo-α'-oleoglycerol (VIII) [d_4^{20} 0.9337, n_D^{20} 1.4772, MR_D 185.70, calculated for $C_{39}H_{70}O_5$ 185.73, iodine number 122.6, calculated 123] in 55 ml of anhydrous chloroform and 5 ml of quinoline at 0° was added 8.72 g of linolenyl chloride. The reaction mass was heated for 4 hr at 54-56° in a nitrogen stream, and cooled to 18-20°. Addition was then made of 75 ml of ether and 70 ml of 0.5 N sulfuric acid. The upper ethereal layer was collected, and from the bottom layer the product was extracted with 40 ml of ether. The combined extracts were washed with saturated aqueous sodium bicarbonate and dried with sodium sulfate. The residue after removal of the solvent was washed with 50 ml of anhydrous methanol. There was obtained 20.4 g of technical triglyceride. Purification was effected by fractional crystallization from 100 ml

* Preceding communication: [1].

of acetone. A precipitate (5.9 g, iodine number 145.2) came down at -35 to -30°. The mother liquor was cooled to -65 to -60°. The resulting crystals were collected (13 g, iodine number 161.4) and again left in 65 ml of acetone at -40 to -35°. The solid phase was filtered off (5.8 g, iodine number 152.4), and the mother liquid cooled to -65 to -60°. The resulting precipitate was collected (1.6 g or 7.04%).

M.p. -(37-35.5) and -(25.5-24)°, d_4^{20} 0.9230, n_D^{20} 1.4791, MR_D 270.20. $C_{57}H_{98}O_6F_6$. Calculated 267.59.

Found %: C 78.18; H 11.41. Iodine number 172.3. $C_{57}H_{98}O_6$. Calculated %: C 77.85; H 11.23. Iodine number 173.2.

α-Linoleo-β-linoleno-α'-palmitin (II). The initial substance, α-linoleo-α'-palmitoglycerol (IX) [m.p. 27-28.2°, iodine number 83.68 (calculated 85.61)], was synthesized from α-monolinoleoglycerol (XI) and palmityl chloride. Reaction was effected between 13.35 g of (IX) and 7.5 g of linolenyl chloride in presence of 60 ml of chloroform and 4 ml of quinoline. The reaction mass was heated for 4 hr at 55-60° and worked up on the lines of the preceding experiment to give 18.5 g of technical triglyceride. This was washed with 50 ml of hot anhydrous methanol, and 13.2 g of product was fractionally crystallized from 66 ml of acetone. The mother liquor after preliminary separation of fractions at -12 to -15°, (iodine number 95.92) and -(15-20)° (iodine number 122.3) was cooled to -(40-35)°. The resulting triglyceride was further purified by passage of the ethereal solution (1 : 10) through a column containing 20 g of alumina and 5 g of active carbon. Yield 4.62 g (23.28%).

M.p. -(14-13)° and -(8-7)°, d_4^{20} 0.9226, n_D^{20} 1.4758, MR_D 269.00. $C_{57}H_{100}O_6F_5$. Calculated 268.15.

Found %: C 78.03, 77.97; H 11.54, 11.37. Iodine number 141.8. $C_{57}H_{100}O_6$. Calculated %: C 77.67; H 11.43. Iodine number 144.

α,α'-Dioleo-β-linolenin (III). The necessary starting substance, α,α'-dioleoglycerol (X) [m.p. 20-21.5°, d_4^{22} 0.9163, n_D^{22} 1.4688, MR_D 188.60 (calculated for $C_{39}H_{72}O_5F_2$ 186.20), iodine number 79.40 (calculated 81.70)], was prepared from α-monooleoglycerol (VI) and oleyl chloride. Reaction was effected between 17.3 g of α,α'-dioleoglycerol and 9.6 g of linolenyl chloride in presence of 60 ml of chloroform and 5 ml of quinoline under the conditions of the preceding experiments. The technical triglyceride (III) (26.93 g) was washed with 75 ml of absolute methanol and subjected to crystallization from 110 ml of acetone. After a precipitate had been separated at -(25-20)° (11.4 g, iodine number 81.23), the mother liquor was cooled to -(55-50)°; the solid phase was filtered off (6.95 g, iodine number 148) and recrystallized from 35 ml of acetone at -(55-50)°. Final purification was effected by filtration of the acetone solution of triglyceride (III) through 9 g of active carbon. Yield 6.95 g (28.31%).

M.p. -48°, -27°, -15°, d_4^{20} 0.9166, n_D^{20} 1.4749, MR_D 270.70. $C_{57}H_{100}O_6F_5$. Calculated 268.15.

Found %: C 77.51, 77.69; H 11.76, 11.52. Iodine number 144.7. $C_{57}H_{100}O_6$. Calculated %: C 77.67; H 11.43. Iodine number 144.

α-Palmito-α',β-dilinolein (IV). To a solution of 14.7 g of α-monopalmitoglycerol (VII) (m.p. 72-73°) in 80 ml of absolute chloroform and 12 ml of quinoline was added 25.65 g of linoleylchloride at 3-5°. The reaction mass was heated at 58-60° for 4 hr in a stream of nitrogen, and then worked up as for the preparation of triglycerides (I) to (III). There was obtained 37 g of technical triglyceride (IV) which was washed with 75 ml of anhydrous methanol with heating to 50°. A solution of 31.8 g of the substance in 150 ml of acetone was filtered through a layer of active carbon (10 g) and alumina (5 g) and subjected to fractional crystallization. The mother liquor, after separation of the solid phase at -(16-14), was cooled to -(40-35)°, and the resulting precipitate (iodine number 109) was again recrystallized at the same temperatures. Yield 5.85 g (15.48%).

M.p. -(6.5-5)°, d_4^{20} 0.9141, n_D^{20} 1.4729, MR_D 261.8. $C_{55}H_{98}O_6F_4$. Calculated 259.28.

Found %: C 77.23, 77.00; H 11.36, 11.40. Iodine number 116.4. $C_{55}H_{98}O_6$. Calculated %: C 77.21; H 11.54. Iodine number 118.7.

α-Palmito-α',β-dilinolenin (V). The synthesis was performed under the conditions of preparation of compound (IV), starting from 3.4 g of α-monopalmitoglycerol (VII) and 9 g of linolenyl chloride in presence of 50 ml of anhydrous chloroform and 3.7 ml of quinoline. The technical triglyceride (V) (6.2 g, iodine number 180) was washed with 45 ml of alcohol at 60° and 70 ml at 18-19°. The solution of the product (5.5 g, iodine number 170) in 50 ml of acetone was filtered through 8 g of active carbon and subjected to crystallization. After separation of solid phase at -15°, the mother liquor was cooled to -40°, and the resulting precipitate recrystallized from acetone at -65°.

For final purification, the triglyceride (V) was passed through a chromatographic column containing alumina (diameter 10 mm, height 120 mm), and eluted with 150 ml of ether. Yield 1.7 g (19.32%).

M.p. -(11-10)°, d_4^{20} 0.9401, n_D^{20} 1.4818, MR_D 258.8. $C_{55}H_{94}O_6F_6$. Calculated 259.2.

Found %: C 77.88; H 11.36. Iodine number 178. $C_{55}H_{94}O_6$. Calculated %: C 77.65; H 11.00. Iodine number 178.8.

SUMMARY

1. The following compounds were synthesized: α-Linoleo-β-linoleno-α'-olein, α-linoleo-β-linoleno-α'-palmitin, α,α'-dioleo-β-linolenin, α-palmito-α',β-dilinolein, and α-palmito-α',β-dilinolenin.

2. The following diglycerides were isolated and characterized in the course of synthesis: α-Linoleo-α'-oleglycerol, α,α'-dioleoglycerol, α-linoleo-α'-palmitoglycerol.

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SYNTHETIC INVESTIGATIONS IN THE FIELD OF CURARE ALKALOIDS

VII. SYNTHESIS OF 2-METHOXY-4-(β-ACYLAMINOETHYL)-2'-ALKOXY-5'-CARBALKOXYMETHYL DIPHENYL ETHERS

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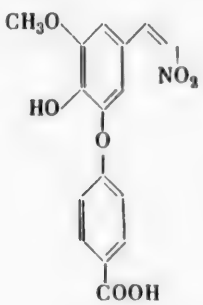
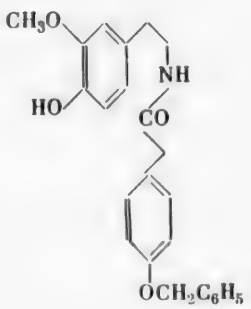
The synthesis of tubocurare alkaloids is complicated by the difficulties of preparation of hydroxyl-containing diphenyl ethers. As was previously reported we realized the synthesis of one of the structural units of these compounds: 2-hydroxy-3-methoxy-5-(β-nitrovinyl)-4'-carboxydiphenyl ether (I) [1]:


(I)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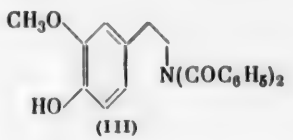
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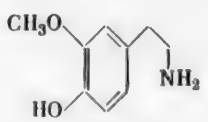
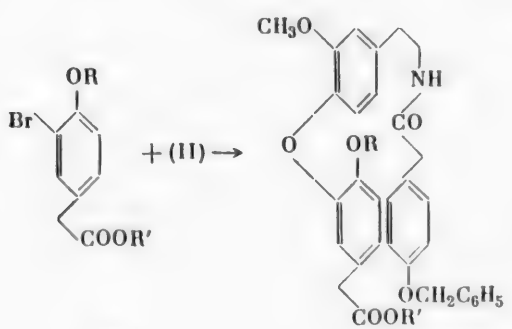

(IV)

Continuing our work in this direction, we have studied methods of preparation of the diphenyl ethers forming the basis of the other portion of the molecule of these alkaloids; it was found that substance containing an aldehyde group give low yields of diphenyl ethers. It was also shown that the β-(3-methoxy-4-hydroxyphenyl)-ethylamide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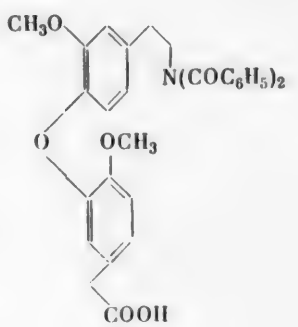
(VI)


(VII)

of 4'-benzyloxyphenylacetic acid (II) and N,N-dibenzoyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine, obtained by fusion of β-(3-methoxy-4-hydroxyphenyl)-ethylamine (IV) with the corresponding acids, do not undergo appreciable modification under the conditions of condensation. We therefore made use of these substances as phenolic

components in the formation of diphenyl ethers which we were able to isolate in good yields. It should be noted that in the preparation of the compounds, in particular those containing an aldehyde group, the yields depend in great measure on the method of preparation of the catalyst. We secured the best results in our experiments [3-6] by use of precipitated copper which had been treated with alcohol and thoroughly dried in vacuo (100° at 10-15 mm).

In this manner, starting from compound (II) and ethyl 3-bromo-4-hydroxyphenylacetate (V, R = H, R'= C_2H_5) we obtained the β-[3-methoxy-4-(2"-hydroxy-5"-carbethoxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (VI, R = H, R' = C_2H_5). The corresponding methyl ester of compound (VI, R = H, R' = CH_3) was formed from substance (II) and (V, R = H, R' = CH_3). Both esters were hydrolyzed to the β-[3-methoxy-4-(2"-hydroxy-5"-carboxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (VI, R = R' = H), which after methylation with diazomethane and hydrolysis was found to be identical with the compound of structure (VI, R = CH_3, R' = H) previously described by us [2]. Both acids (VI) (R = R' = H and R = CH_3, R' = H) and amide (II) were isolated in dimorphic forms which were sometimes formed simultaneously. Previous shielding of the phenolic hydroxyl in bromoester (V, R = H, R' = CH_3) with chloromethyl ether to form the methyl ester of 3-bromo-4-methoxymethoxyphenylacetic acid (V, R = CH_3OCH_2, R' = CH_3) did not lead to increased yield of the resulting diphenyl ether (VI) (R = CH_3OCH_2, R' = H). From compounds (III) and (V) (R = R' = CH_3) was synthesized N,N-dibenzoyl-β-[3-methoxy-4-(2'-methoxy-5'-carboxymethylphenoxy)-phenyl]-ethylamine (VII).

Esters of 3-boromo-4-hydroxy-(or methoxy)-phenylacetic acids (V, R = H or CH_3, R' = CH_3, C_2H_5) were prepared by bromination of the respective 4-substituted phenylacetic acids with dioxane dibromide and subsequent esterification in the usual manner.

EXPERIMENTAL

β-(3-Methoxy-4-hydroxyphenyl)-ethylamide of 4'-benzyloxyphenylacetic acid (II) was obtained in nearly quantitative yield by fusion of β-(3-methoxy-4-hydroxyphenyl)-ethylamine with 4-benzyloxyphenylacetic acid. M.p. 110-111°(from alcohol) (111-113° [7]).

Found %: C 73.34; H 6.42; N 3.61. $C_{24}H_{25}O_4N$. Calculated %: C 73.60; H 6.43; N 3.58.

A second recrystallization from benzene or carbon tetrachloride gave a substance with m.p. 124-125°.

Found %: C 73.49; H 6.42; N 3.56. $C_{24}H_{25}O_4N$. Calculated %: C 73.60; H 6.43; N 3.58.

The sample with m.p. 110-111° melted at 122-124° after fusion and rapid crystallization. A mixture of the two forms does not exhibit a depression of melting point.

β-[3-Methoxy-4-(2"-hydroxy-5"-carbalkoxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (VI). a) (VI, R = H, R' = C_2H_5). A solution of 7 g of the β-(3-methoxy-4-hydroxyphenyl)-ethylamide of 4'-benzyloxyphenylacetic acid (m.p. 124-125°) in potassium methoxide (from 0.73 g of potassium and 20 ml of methyl alcohol) was prepared by heating on a water bath, the alcohol was distilled off, and the residue dried in vacuo (105-110°, 8 mm, 3 hr). To the thoroughly pulverized phenate were added 8 g of ethyl 3-bromo-4-hydroxyphenylacetate (m.p. 44-45°) and 7 g of copper powder. The mixture was stirred for 90 min in a nitrogen stream at 180-190°. After cooling, the reaction mass was well triturated in succession with ether (8 times with 50 ml each) and with boiling benzene (3 times with 50 ml each) for removal of unreacted bromoester and amide. The residue was dissolved in acetone or chloroform (330 ml), the copper and potassium bromide were filtered off, and the solvent was removed in vacuo. There was obtained 6.35 g (62.1%). M.p. 99-102°.

Found %: N 2.21, 2.33. $C_{34}H_{35}O_7N$. Calculated %: N 2.46.

Some experiments led to a substance with m.p. 65-67° (after purification over alumina). Yield 61.1%.

Found %: C 71.38; H 6.14; N 2.68, 2.36. $C_{34}H_{35}O_7N$. Calculated %: C 71.2; H 5.95; N 2.52.

b) (VI, R = H, R' = CH_3). Similarly prepared from compound (V) and methyl 3-bromo-4-hydroxyphenylacetate. M.p. 102-105°.

Found %: C 71.20; H 6.00; N 2.61, 2.63. $C_{33}H_{33}O_7N$. Calculated %: C 71.30; H 5.94; N 2.52.

β-[3-Methoxy-4-(2"-hydroxy-5"-carboxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (VI, R = R' = H). A mixture of 7.02 g of the β-[3-methoxy-4-(2"-hydroxy-5"-carbethoxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid, 2 g of sodium carbonate, 10 ml of water, and 30 ml of alcohol was boiled for 3 hr. The alcohol was distilled in vacuo; the residue was dissolved in 50 ml of water, filtered,

and precipitated with dilute (1 : 1) hydrochloric acid. The precipitated substance was collected, washed with water until neutral, and dried. It was then dissolved in acetone and filtered. The solvent was taken off in vacuo to leave 6.32 g (94.8%) of product. M.p. 136-138°.

Found %: C 71.20; H 5.63; N 2.51, 2.73. $C_{32}H_{33}O_7N$. Calculated %: C 71.00; H 5.74; N 2.59.

Hydrolysis of a specimen with m.p. 65-67° gave an acid with m.p. 83.5-85°.

Found %: C 71.22; H 5.74; N 2.35, 2.27.

β-[3-Methoxy-4-(2"-methoxy-5"-carboxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (VI, R = CH_3, R' = H). To a solution of 0.5 g of the β-[3-methoxy-4-(2"-hydroxy-5"-carboxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (m.p. 136-138°) in 120 ml of methyl alcohol was stirred at 20° an ethereal solution of diazomethane prepared from 5 g of nitrosomethylurea. The solution was allowed to stand for 20 hr at 20°. After removal of the solvent, the dimethyl derivative (VI, R = R' = CH_3) remained behind. Yield 0.38 g (72.5%). M.p. 90-96°.

Found %: N 2.64. $C_{34}H_{35}O_7N$. Calculated %: N 2.46.

Hydrolysis with aqueous alcoholic sodium carbonate solution gave the acid (VI, R = CH_3, R' = H). Yield 89.2%. M.p. 104-106°.

Found %: N 2.69, 2.47. $C_{33}H_{33}O_7N$. Calculated %: N 2.52.

The substance did not exhibit a depression of melting point in admixture with a specimen earlier prepared from compound (II) and ethyl 3-bromo-4-methoxyphenylacetate with m.p. 107-108° [2].

Found %: C 71.66; H 5.73; N 2.48, 2.65. $C_{33}H_{33}O_7N$. Calculated %: C 71.30; H 5.94; N 2.52.

In some of the experiments on hydrolysis of ester (VI, R = R' = CH_3) prepared by condensation of compounds (II and V, R = R' = CH_3), the more easily soluble form was obtained. M.p. 66-68°.

Found %: C 71.38; H 5.77; N 2.49. $C_{33}H_{33}O_7N$. Calculated %: C 71.30; H 5.94; N 2.52.

β-[3-Methoxy-4-(2"-methoxymethoxy-5"-carboxymethylphenoxy)-phenyl]-ethylamide of 4'-benzyloxyphenylacetic acid (VI, R = CH_2OCH_3, R' = H). In 35 ml of anhydrous methanol was dissolved 0.42 g of potassium, and then 3.5 g of β-(3-methoxy-4-hydroxyphenyl)-ethylamide of 4'-benzyloxyphenylacetic acid. The alcohol was taken off in vacuo; the residue was dried at 15 mm and 110-120° for an hour, after which it was pulverized. Addition was then made of 6.55 g of methyl 3-bromo-4-methoxymethoxyphenylacetate and 3.5 g of copper powder. The reaction mass was stirred for 50 min at 190-200°, cooled, and extracted with 150-200 ml of ether; the residue was dissolved in 150 ml of chloroform and the solution filtered from copper and potassium bromide. The chloroform was distilled off, and the amorphous residue (4.5 g) hydrolyzed with 7 g of potassium carbonate, 15 ml of water, and 30 ml of methyl alcohol (5 hr at the boil). The reaction mass was concentrated in vacuo, and the residue was dissolved in 100 ml of water, filtered, and acidified with 15 ml of dilute (1 : 1) hydrochloric acid. The precipitated substance was separated, washed with water (100 ml), and dried (weight 3.14 g). The product was treated with boiling benzene (125 ml) until the extract was no longer colored. After removal of solvent and trituration of the residue with ether, there was obtained 0.5 g of unreacted amide (0.5 g, m.p. 108-109°). The benzene-insoluble portion was treated with 130 ml of chloroform, and evaporation of the solution gave a light-yellow substance. Yield 2.48 g (47.22%). M.p. 103-115°.

Found %: C 69.61; H 5.97; N 2.44. $C_{34}H_{35}O_8N$. Calculated %: C 69.74; H 5.99; N 2.39.

N,N-Dibenzoyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine (III). A mixture of 2.66 g of β-(3-methoxy-4-hydroxyphenyl)-ethylamine and 1.95 g of benzoic acid was heated for an hour in a nitrogen stream with stirring at 180-195°. The reaction mass was thoroughly triturated with ether (200 ml) until the extract was no longer colored. The mass was separated by decantation, dried, and twice recrystallized from dilute (1 : 1) alcohol and then from carbon tetrachloride. Yield 1.6 g (37.2%). M.p. 105-106°.

Found %: C 73.9, 73.8; H 5.75, 5.27; N 3.47, 3.45. $C_{23}H_{21}O_4N$. Calculated %: C 73.6; H 5.61; N 3.74.

N,N-Dibenzoyl-β-[3-methoxy-4-(2'-methoxy-5'-carboxymethylphenoxy)-phenyl]-ethylamine (VII). To a solution of 0.31 g of potassium hydroxide in 20 ml of methanol was added 1.5 g of N,N-dibenzoyl-β-(3-methoxy-4-

hydroxyphenyl)-ethylamine, and the alcohol was taken off in vacuo. Addition was then made of 1.44 g of methyl 3-bromo-4-methoxyphenylacetate and 1.5 g of copper powder. The mixture was stirred in a stream of nitrogen for an hour at 195-205°. After cooling, the reaction mass was treated with ether (ten lots of 20 ml each). The residue was dissolved in 40 ml of chloroform and the solution filtered from copper and potassium bromide. The solvent was removed in vacuo. The amorphous residue was hydrolyzed with 3 g of sodium carbonate, 10 ml of water, and 40 ml of methyl alcohol (1.5 hr at the boil). The alcohol was taken off in vacuo, and the residue was dissolved in 70 ml of water; the solution was filtered and the acid isolated by treatment with dilute (1 : 1) hydrochloric acid. The substance was purified by extraction with boiling alcohol and then (after removal of solvent) with alcohol. The alcoholic extracts were concentrated and the product again precipitated from alkali solution with acid. M.p. 80-87°.

Found %: C 71.4, 71.43; H 5.99, 6.01; N 2.71. $C_{32}H_{29}O_7N$. Calculated %: C 71.3; H 5.45; N 2.60.

3-Bromo-4-methoxyphenylacetic acid (V, R = CH_3, R' = H). To 230 g of 4-methoxyphenylacetic acid was added 346 g of dioxane dibromide with vigorous stirring, and stirring was continued until the red color of the fused reaction mass no longer changed to orange (10 min). It was then heated for 15 min at 70-75°, 400 ml of ice water was added, and the precipitate filtered off, washed with water (three lots of 100 ml each), and dried. Yield 294.5 g (86.9%). M.p. 113-114.5° (from alcohol).

The ethyl ester was prepared by the method of azeotropic esterification. Yield 92.6%. B.p. 142-144° (3 mm).

Methyl ester: b.p. 144-145° (3 mm). M.p. 45-47° (from a mixture of ether and ligroine, 1 : 3).

3-Bromo-4-hydroxyphenylacetic acid (V, R = R' = H). The method of preparation was similar to that for bromination of 4-hydroxyphenylacetic acid (with dioxane dibromide in acetic acid). Yield 74.3%. M.p. 105-107° (from chloroform or carbon tetrachloride).

Ethyl ester: yield 84.5%; b.p. 106.5-107° (0.15 mm); m.p. 44-45°.

Methyl ester: b.p. 137-139° (2.5 mm); m.p. 75-77° (from a 5 : 1 mixture of ligroine and carbon tetrachloride).

Methyl 3-bromo-4-methoxymethoxyphenylacetate (V, R = CH_2OCH_3, R' = CH_3). A solution of 16.7 g of methyl 3-bromo-4-hydroxyphenylacetate (b.p. 137-139° at 2.5 mm) was prepared in sodium methoxide (from 1.65 g of sodium and 60 ml of methanol), and the methanol was taken off in vacuo. The resulting crystalline phenate was suspended in 100 ml of absolute ether and cooled to -10°, and then 6.4 g of chloromethyl ether (90% purity) was stirred in. The mixture was held for an hour at -(10-5)°, 3 hr at -(5-1)°, and 15 hr at 10-20°; 40 ml of 5% potassium hydroxide was added, and the ether layer separated, washed with water (three lots of 20 ml each), and dried with sodium sulfate before being distilled. Yield 15.2 g (77.8%). B.p. 128-130° (3 mm).

Found %: Br 29.09. $C_{11}H_{13}O_4Br$. Calculated %: Br 29.05.

SUMMARY

A number of 2-methoxy-4-(β-acylaminoethyl)-2'-alkoxy-5'-carbalkoxymethyl diphenyl ethers (intermediates for tubocurare alkaloids) were prepared. The possibility was shown of preparation of such compounds in good yields by the Ullmann condensation without protection of the phenolic hydroxyls.

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SYNTHESIS OF 4,7,9,12-HEXADECATETRAYNE-1,16-DICARBOXYLIC ACID

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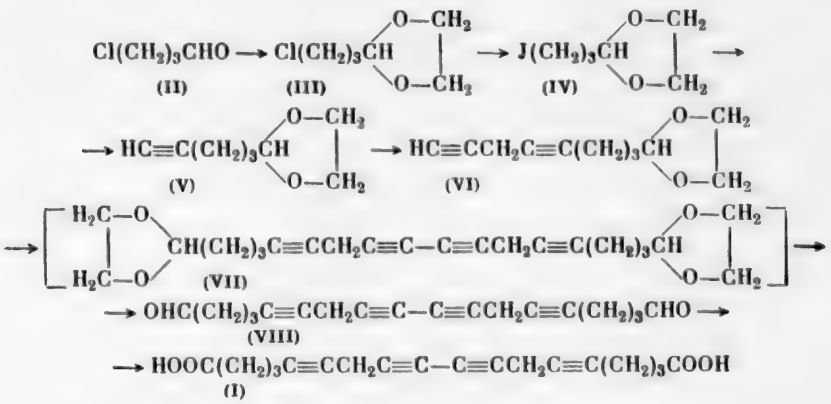
In continuation of our investigations [1] on the synthesis of higher polyunsaturated acids of the aliphatic series [2], we have developed a method of preparation of 4,7,9,12-hexadecatetrayne-1,16-dicarboxylic acid (I).



Oxidative coupling [3] of 2-(4',7'-octadiynyl)-1,3-dioxolane (VI) gave the diethyleneacetal of 5,8,10,13-octadecatetraynedial (VII) which leads to 5,8,10,13-octadecatetraynedial (VIII). The latter is then oxidized to 4,7,9,12-hexadecatetrayne-1,16-dicarboxylic acid (I). The starting materials for 2-(4',7'-octadiynyl)-1,3-dioxolane (VI) are propargyl bromide [4] and 2-(4'-pentynyl)-1,3-dioxolane (V). The latter is prepared from γ-chlorobutyraldehyde (II) with intermediate formation of 2-(γ-chloropropyl)-1,3-dioxolane (III) and 2-(γ-iodopropyl)-1,3-dioxolane (IV).

EXPERIMENTAL

2-(γ-Chloropropyl)-1,3-dioxolane (III). Hydrogen was passed through a boiling mixture of 35 g of γ-chlorobutyryl chloride [5], 200 ml of toluene, and 3.5 g of palladium on barium sulfate [6] until hydrogen evolution ceased [7]. The catalyst was separated and 0.5 ml of concentrated sulfuric acid and 40 ml of ethylene glycol were stirred into the filtrate at 18-20°. The resulting mass was boiled for 4 hr [8]. The solvent was removed and the residue distilled. Yield 23.9 g (64.2%).

B.p. 78-79° (10 mm), d_4^{20} 1.1520, n_D^{20} 1.4548, MR_D 35.45; calc. 35.91.

Found %: C 47.68; H 7.07. $C_6H_{11}O_2Cl$. Calculated %: C 47.80; H 7.33.

2-(γ-Iodopropyl)-1,3-dioxolane (IV). A mixture of 30 g of 2-(γ-chloropropyl)-1,3-dioxolane, 200 ml of acetone, and 45 g of sodium iodide was boiled for 12 hr. The reaction mass was then cooled to 18-20° and the precipitate was separated. After removal of the solvent, the residue was distilled. Yield 29.9 g (62.1%).

B.p. 69-70° (0.6 mm), d_4^{20} 1.6971, n_D^{20} 1.5248, MR_D 43.72; calc. 43.79.

Found %: C 30.20; H 4.10. $C_6H_{11}O_2I$. Calculated %: C 29.75; H 4.54.

2-(4'-Pentynyl)-1,3-dioxolane (V). In the course of 10 min 8.1 g of 2-(γ-iodopropyl)-1,3-dioxolane (IV) in 30 ml of ether was added to sodium acetylide prepared from 1.1 g of sodium and excess of acetylene in 300 ml of liquid ammonia. The reaction mixture was stirred for 5 hr and allowed to stand for 12 hr at 18-20°. Addition was then made of 100 ml of ether and 30 ml of water, the ether layer was separated, and the aqueous layer extracted with ether (two lots of 25 ml each). The combined extracts were dried with sodium sulfate. After removal of the solvent, the residue was distilled to give 3.71 g (80.1%) of product.

B.p. 68-69° (8 mm), d_4^{20} 0.9971, n_D^{20} 1.4540, MR_D 38.07. $C_8H_{12}O_2F$. Calculated 38.16.

Found %: C 68.78; H 8.30. $C_8H_{12}O_2$. Calculated %: C 68.57; H 8.62.

2-(4',7'-Octadiynyl)-1,3-dioxolane (VI). In the course of 10 min 4.1 g of 2-(4'-pentynyl)-1,3-dioxolane (V) was added to ethylmagnesium bromide prepared from 0.61 g of magnesium and 2.8 g of ethyl bromide in 50 ml of absolute ether. The mixture was boiled for 2 hr, 0.5 g of cuprous chloride and 3.2 g of propargyl bromide were added, and heating was continued for 10 hr. The mass was then cooled to 18-20° and the precipitate collected. After removal of solvent, the residue was distilled to give 1.81 g (34.6%).

B.p. 78-80° (0.5 mm), d_4^{20} 0.9908, n_D^{20} 1.4730, MR_D 50.40. $C_{11}H_{14}O_2F_2$. Calculated MR_D 50.08.

Found %: C 73.93; H 8.10. $C_{11}H_{14}O_2$. Calculated %: C 74.13; H 7.92.

5,8,10,13-Octadecatetraynedial diethyleneacetal (VII). A stream of dry air was passed for 30 min through a mixture of 400 ml of liquid ammonia and 4.3 g of 2-(4',7'-octadiynyl)-1,3-dioxolane (VI). The reaction mass was stirred for 4 hr, 100 ml of ether was added, and the mass allowed to stand for 12 hr at 18-20°. Addition was then made of 30 ml of water, the ethereal layer collected, and the aqueous layer extracted with ether (two lots of 20 ml each). The combined extracts were dried with sodium sulfate. After removal of the solvent, the residue was distilled to give 2.4 g (56.2%). B.p. 110-111° (0.08 mm).

5,8,10,13-Octadecatetraynedial (VIII). Into a solution of 1.6 g of potassium iodate and 0.7 ml of sulfuric acid (d 1.84) in 100 ml of water, heated to 80-85°, was run 2.3 g of 5,8,10,13-octadecatetraynedial diethyleneacetal (VII) in 250 ml of dioxane. The reaction mass was heated to boiling, allowed to stand for 3 hr at 18-20°, and neutralized with saturated aqueous sodium bicarbonate solution. The resulting product was extracted with ether (three lots of 40 ml each). The combined extracts were dried with magnesium sulfate, and the solvent taken off to leave 1.56 g of yellow, oily liquid.

The 2,4-dinitrophenylhydrazone had m.p. 136-137° (from alcohol).

Found %: N 18.20. $C_{30}H_{26}O_8N_8$. Calculated %: N 17.88.

4,7,9,12-Hexadecatetrayne-1,16-dicarboxylic acid (I). To 60 ml of alcoholic solution of 2.5 g of silver nitrate was added 1.36 g of (VIII) in 20 ml of alcohol, followed in the course of 10 min by a solution of 1.2 g of sodium hydroxide in 40 ml of alcohol. The reaction mixture was stirred for 9 hr at 18-20°, the precipitate filtered off, and the solvent removed. To the residue was added 30 ml of water, the unreacted (VIII) extracted with eth (three lots of 30 ml each), the aqueous layer acidified with 6 N hydrochloric acid (pH 5 by universal indicator), and the reaction product extracted with ether (four lots of 30 ml each). The extract was dried with magnesium sulfate. After removal of the solvent, 0.6 g of crystalline product was obtained. M.p. 80-81°.

Found %: C 72.88; H 5.97. $C_{18}H_{18}O_4$. Calculated %: C 72.46; H 6.08.

SUMMARY

4,7,9,12-Hexadecatetrayne-1,16-dicarboxylic acid was synthesized.

The following substances were isolated during the synthesis: 2-(γ-chloropropyl)-1,3-dioxolane, 2-(γ-iodopropyl)-1,3-dioxolane, 2-(4'-pentynyl)-1,3-dioxolane, and 5,8,10,13-octadecatetrayndial (characterized as the 2,4-dinitrophenylhydrazone).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

PREPARATION OF STABLE 4,5,5-TRIMETHYL-2-PHENYL-2,5-DIHYDROFURYLIUM SALTS

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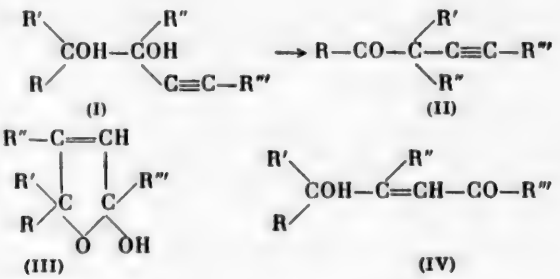
Conversion of ditertiary acetylenic α-glycols (pinacones), containing a substituted acetylenic hydrogen (I), in presence of dilute sulfuric acid has been studied by É. D. Venus-Danilova and co-workers in connection with a number of compounds [1-4]. It was found that these glycols, apart from forming acetylenic ketones (II), can isomerize into substituted 2-hydroxy-2,5-dihydrofurans (III) or into the tautomeric forms of the latter–unstable olefinic γ-ketoalcohols (IV). 2-Hydroxy-2,5-dihydrofurans, not previously described in the literature, possess basic properties [5-7] and are five-membered analogs of pyrilium salts.

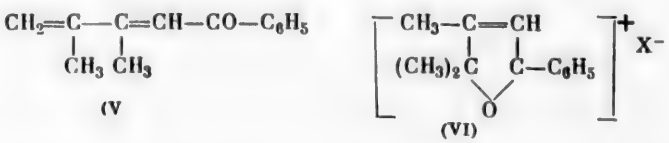


The products of transformation and the percentage ratio of the resulting substances depend on the nature of the substituents R–R‴ and on their relative positions in the glycol molecule.

One of the acetylenic pinacones (I) whose behavior under the action of sulfuric acid has been studied is trimethylphenylethynylethylene glycol (I, R, R', R" = CH_3; R‴ = C_6H_5) [8].

Products isolated from the acid solution after treatment of this glycol with sulfuric acid were an acetylenic ketone (II, R, R', R" = CH_3, R‴ = C_6H_5) and a mixture of olefinic γ-ketoalcohol (IV, R, R' = CH_3, R‴ = C_6H_5) and dienic ketone (V). After neutralization of the sulfuric acid, ethylideneacetophenone and acetone were detected–products of ketonic cleavage of the olefinic γ-ketoalcohol. The latter could not be isolated in the pure state. The same was true of the substituted 2-hydroxy-2,5-dihydrofuran (III, R, R', R" = CH_3, R‴ = C_6H_5).

Somewhat later É. D. Venus-Danilova and the author of this paper [9] prepared the stable complex salt (VI, X = $HgCl_3$) by reaction of the glycol with mercuric chloride in presence of hydrochloric acid.



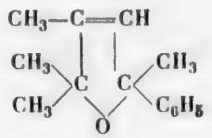
It may therefore be assumed that 4,5,5-trimethyl-2-phenyl-2-hydroxy-2,5-dihydrofuran breaks down only in a neutral or weakly alkaline medium, whereas it can exist in acid solution in the form of 2,5-dihydrofurylium salts. Isolation and study of such salts present considerable interest since–by analogy with pyrilium salts [10] and salts of

oxyphthalans [11]—we can expect an enhanced mobility of the hydrogen atoms of the methyl group in the 4 position of the dihydrofuran ring and consequently the ability to undergo various condensations.

In the present paper is described the preparation of some simple and complex salts corresponding to 4,5,5-trimethyl-2-phenyl-2-hydroxy-2,5-dihydrofuran.

Addition of perchloric acid to the sulfuric acid solution of the product of interaction of this glycol (without prior isolation) led to separation of the perchlorate (VI, X = ClO_4); the hydrochloric acid solution of the product of interaction of the glycol forms a complex ferrichloride (VI, X = $FeCl_4$). The stannichloride $(C_{13}H_{15}O)_2SnCl_6$ and platinichloride $(C_{13}H_{15}O)_2PtCl_6$, corresponding to 2-hydroxy-2,5-dihydrofuran (IV), were also prepared.

Treatment of 2-hydroxy-2,5-dihydrofuran perchlorate with excess of ethereal solution of methylmagnesium iodide by the earlier procedure [5, 6] led to synthesis of 2,2,3,5-tetramethyl-5-phenyl-2,5-dihydrofuran (VII). This result again confirms the presence of the 2,5-dihydrofuran ring in the salts obtained.



(VII)

Attempts were made to isolate the free 4,5,5-trimethyl-2-phenyl-2-hydroxy-2,5-dihydrofuran. With the objective of eliminating the strongly alkaline medium, which could lead to decomposition of 2-hydroxy-2,5-dihydrofuran, the sulfuric acid solution (obtained after heating of the acetylenic pinacone with sulfuric acid), in which the hydroxydihydrofuran is present as the sulfate, was neutralized with sodium carbonate. The pH of the solution was thereby brought down to about 6. But even under these conditions the hydroxydihydrofuran broke down and only ethylideneacetophenone and acetone were obtained.

No success likewise attended an attempt at reduction of the sulfuric acid solution of the dihydrofurylium salt with zinc or tin chloride in presence of iodine, although this technique had been successful in the case of benzopyrillium and xanthilium salts [12, 13].

The 2,4-dinitrophenylhydrazone of the ethylenic γ-ketoalcohol (IV, R, R', R" = CH_3, R"' = C_6H_5), isomeric with 4,5,5-trimethyl-2-phenyl-2-hydroxy-2,5-dihydrofuran, was likewise not isolated when the sulfuric acid solution of the hydroxydihydrofuran was treated with 2,4-dinitrophenylhydrazine [14].

4,5,5-Trimethyl-2-phenyl-2-hydroxy-2,5-dihydrofuran is consequently not stable and can exist only in the form of salts. The corresponding ethylenic γ-ketoalcohol breaks down in the instant of formation to benzylideneacetophenone and acetone, or undergoes dehydration to the dienic ketone.

EXPERIMENTAL

1. 4,5,5-Trimethyl-2-phenyl-2,5-dihydrofurylium perchlorate. a) Trimethylphenylphenylethynylethylene glycol (20.4 g) was heated with 35% sulfuric acid (200 ml) for an hour at the boil and with stirring. After removal of neutral reaction products and resinous impurities, addition was made to the sulfuric acid solution of 10 ml of 70% perchloric acid in the cold. Nearly colorless crystals at once came out and were filtered and washed with perchloric acid. Recrystallization from glacial acetic acid gave 7.5 g (26.6%) of colorless crystals which turned green when kept; m.p. 135-136° (decomp.).

Found %: C 54.36; H 5.38; Cl 12.26, 12.30. $C_{13}H_{15}O_5Cl$. Calculated %: C 54.45; H 5.24; Cl 12.35.

b) The only difference between this experiment and the preceding one was that 0.5 g of yellow mercuric oxide was added to the same quantities of acetylenic glycol and sulfuric acid. Recrystallization of the resulting yellow precipitate gave 11.5 g (40.1%) of colorless perchlorate crystals with m.p. 135-136° (decomp.).

2. The ferrichloride was synthesized from 20.4 g of acetylenic glycol by heating with 100 ml of 20% hydrochloric acid, separating off the neutral substances, and adding to the acid solution an excess of ferric chloride. The greenish-yellow ferrichloride came down at once; m.p. 84-85° (from glacial acetic acid, decomp.).

Found %: Fe 14.38, 14.46; Cl 36.63, 36.91. $C_{13}H_{15}OCl_4Fe$. Calculated %: Fe 14.50; Cl 36.83.

3. Platinichloride. This salt came down slowly in the course of 24 hr when the 2,5-dihydrofurylium solution in hydrochloric acid of experiment 2 was treated with platinic chloride. Well-formed orange crystals with m.p. 183-184° (decomp.).

Found %: Pt 24.99, 25.08; Cl 27.16, 27.21. $C_{26}H_{30}O_2Cl_6Pt$. Calculated %: Pt 24.95; Cl 27.12.

4. Stannichloride. Prepared similarly to the platinichloride. Recrystallization from glacial acetic acid gave pale-yellow crystals with m.p. 205-206° (decomp.). This salt is very much less soluble than the preceding one in glacial acetic acid.

Found %: Sn 16.96, 17.01; Cl 30.08, 30.11. $C_{26}H_{30}O_2Cl_6Sn$. Calculated %: Sn 16.81; Cl 30.16.

5. 2,2,3,5-Tetramethyl-5-phenyl-2,5-dihydrofuran (VII). With external cooling and with stirring, 10 g of 4,5,5-trimethyl-5-phenyl-2,5-dihydrofuran was added in three portions to an ethereal solution of methylmagnesium iodide prepared in the usual manner from 2 g of magnesium. After the whole of the perchlorate had been added, the reaction mass was heated for 0.5 hr (gentle boiling of the ether), and after cooling it was decomposed with aqueous ammonium chloride solution. After the usual working-up, the product was distilled in vacuo to give 6 g (82.5%) of a colorless liquid with a pleasant odor of camphor and mint. The compound does not contain hydroxyl or carbonyl groups and is insoluble in acids. It reacts fairly slowly with bromine in chloroform and with aqueous potassium permanganate.

B.p. 114-115° (13 mm), n_D^{20} 1.5102, d_4^{20} 0.9906, MR_D 61.09. $C_{14}H_{18}O_4$. Calculated 62.21.

Found %: C 83.10, 83.04; H 8.74, 8.89. M 211. $C_{14}H_{18}O$. Calculated %: C 83.12; H 8.97. M 202.2.

Judging by the analysis and its properties, the product is 2,2,3,5-tetramethyl-5-phenyl-2,5-dihydrofuran (not previously described).

The compound was oxidized with potassium permanganate with the aim of confirming its structure. For 4 g of the substance (b.p. 114-115° at 13 mm) 10.4 g of oxidizing agent (equivalent to 10 moles of oxidizing agent for 3 moles of substance) was taken. To 300 ml of 2% aqueous potassium permanganate solution was added the whole quantity of 2,5-dihydrofuran derivative in a single portion. The remainder of the oxidant was introduced into the reaction mass in the form of a fine powder. Heating of the reaction mass for 8 hr at 40° was necessary due to the slowness of oxidation. Throughout the whole operation the mass was intensively stirred. After decolorization had taken place, 0.5 g of sodium carbonate was added and the manganese dioxide was separated by filtration. The filtrate was extracted several times with ether and the extracts combined with the ether used for washing the manganese dioxide. After drying and removal of the ether, the residual liquid weighed 1.5 g and had the odor of acetophenone. It gave acetophenone 2,4-dinitrophenylhydrazone with m.p. 249-250° (mixed melting test). The acetophenone content of the mixture of neutral oxidation products was about 60%; the remainder was probably unoxidized dihydrofuran derivative. The aqueous solution remaining after extraction with ether was distilled on a water bath and gave acetone in the form of its 2,4-dinitrophenylhydrazone with m.p. 124-125° (mixed melting test).

Subsequently the alkaline solution of the salts of organic acids was concentrated on a water bath and decomposed with dilute sulfuric acid. Among the steam-volatile acids were detected formic acid (test with mercuric chloride and an ammoniacal silver oxide), benzoic acid (sublimation and mixed melting test), and acetic acid (silver salt prepared).

Found %: Ag 63.95. $C_2H_3O_2Ag$. Calculated %: Ag 64.65.

After the steam-volatile acids had been removed, the residue was extracted with ether and yielded a viscous mass from which gradually separated crystals with a honey-like odor. After purification on porous plate, the crystals melted at 65-67°. Judging from the melting point and by analogy with the acid isolated after oxidation of 2,5,5-trimethyl-2,4-diphenyldihydrofuran [5], this acid is methylphenylglycolic acid. Its silver salt could not be prepared due to the smallness of the quantity.

SUMMARY

1. It was established that 4,5,5-trimethyl-2-phenyl-2-hydroxy-2,5-dihydrofuran (unknown in the free state) forms stable dihydrofurylium salts – perchlorate, ferrichloride, stannichloride, and platinichloride.

2. Reaction of the dihydrofurylium perchlorate with methylmagnesium iodide gave the previously undescribed 2,2,3,5-tetramethyl-2-phenyl-2,5-dihydrofuran. This reaction confirmed the presence of a dihydrofuran ring in 4,5,5-trimethyl-2-phenyl-2,5-dihydrofurylium salts.

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SOME NEW MODIFICATIONS OF THE ARBUZOV REARRANGEMENT

XII. ACTION OF MERCURIC ACETATE ON TRIALKYL PHOSPHITES*

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 5,
pp. 1552-1553, May, 1961
Original article submitted May 23, 1960

In earlier papers one of us in collaboration with G. Kamai [1, 2] had shown that organic acids and their anhydrides can react with trialkyl phosphites in accordance with the Arbuzov rearrangement. It seemed of interest to us to establish whether salts of organic acids, in particular mercury salts, are capable of promoting the Arbuzov rearrangement. V. S. Abramov had shown [3] that inorganic halides can interact with trialkyl phosphites in a similar manner to alkyl halides:

$$(RO)_3P + LiCl \longrightarrow (RO)_2P\overset{O}{\underset{Li}{<}}$$

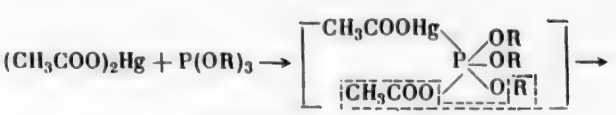
The action of mercuric acetate of trialkyl phosphites was studied by I. F. Lutsenko, R. M. Khomutova, and L. A. Eliseeva [4]. In their opinion the following mechanism is involved [5]:

$$(CH_3COO)_2Hg + P(OR)_3 \longrightarrow Hg + [(CH_3COO)_2P(OR)_3] \longrightarrow 2CH_3COOR + (ROPO_2)_x$$

The authors of the above paper observed the separation of mercury and formation of alkyl acetate; they did not clarify the fate of the phosphoric component.

We examined the reaction of mercuric acetate with triethyl phosphite under milder conditions: We gradually added the mercuric acetate in such a way that the temperature did not exceed 40-45° during the reaction. The reaction mass turned gray during the reaction, evidently due to separation of metallic mercury. The reaction products were extracted with benzene for the purpose of freeing them from mercury and its oxide compounds; after removal of the benzene and ethyl acetate, we obtained diethoxyphosphinylmercuric acetate.

Hence mercuric acetate and triethyl phosphite evidently only in part interact in accordance with the scheme proposed by Lutsenko and co-workers; under mild conditions in particular, the reaction in part proceeds by the Arbuzov rearrangement.



$$CH_3COOHgP(OR)_2 + CH_3COOR$$
$$\|$$
$$O$$

Other phosphites react similarly to triethyl phosphite. Melting points and yields of products are presented in the table.

* The preceding communications of this series were published under the main heading of "Addition of full esters of phosphorous and phosphonous acids to conjugated systems."

Dialkoxyphosphinylmercuric Acetates

R	Melting point	Yield (%)	Melting points reported in the literature [6]
C_2H_5	105—106.5°	37	106.8—107.6°
n.-C_3H_7	85.5—87.5	21	86.3—87.2
iso -C_3H_7	146—147	39	146.2—146.8
n.-C_4H_9	80—81	25	80.5—81.1

EXPERIMENTAL

Reaction of mercuric acetate with triethyl phosphite. To 7.95 g of triethyl phosphite was added 15.7 g of mercuric acetate in small portions at such a rate that the temperature of the reaction mixture did not exceed 45° (addition of one-half of the calculated quantity of mercuric acetate in a single portion caused the temperature to rise to 120°). The salt dissolved nearly completely. After one hour had elapsed since completion of addition of the salt, the viscous, gray liquid crystallized. Solution was accelerated by addition of benzene (40 ml) while heating was continued at 40-50°. After 24 hr, the benzene solution was decanted from the gray mass of mercury and its oxides. Even after 24 hr a little more gray, dust-like precipitate appeared; after removal of the latter, the benzene and ethyl acetate were distilled in vacuo (towards the end at a temperature of 40-50°). After standing in a refrigerator overnight, colorless needles came down. These were separated by filtration and washed with ligroine; the filtrate and wash liquor were combined and again allowed to stand in the refrigerator. In this way a fresh crop of crystals was obtained. Total yield 7.10 g (37%), m.p. 105-106.5° (from a mixture of benzene and ether or a little benzene). The literature [6] gives m.p. 106.8-107.6°. Other dialkoxyphosphinylmercuric acetates were prepared in similar fashion (see table). Products in which R = n-C_3H_7 or n-C_4H_9 do not crystallize from the reaction mixture. More prolonged standing in the refrigerator was needed for their crystallization after removal of the benzene.

SUMMARY

The action of mercuric acetate on trialkyl phosphites was studied, and it was shown that reaction between them can proceed in accordance with the Arbuzov rearrangement.

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SOME DIALKYLMALONIC ESTERS

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 5,
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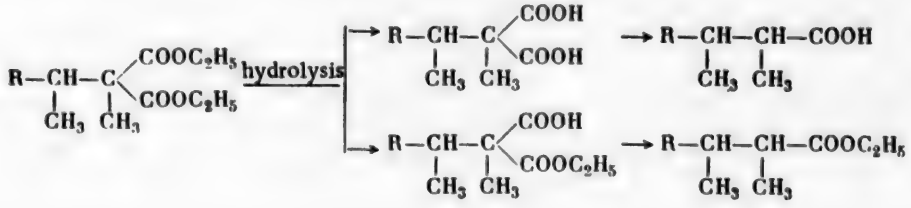
We previously reported on the synthesis of monoalkylmalonic esters of the formula $RCH(CH_3)CH(COOC_2H_5)_2$ by addition of organomagnesium compounds to ethylidenemalonic ester [1]. In the course of further investigations we synthesized a series of dialkylmalonic esters of the formula $RCH(CH_3)C(CH_3)(COOC_2H_5)_2$.

According to the literature, monoalkylmalonic esters containing secondary alkyl radicals are not easily alkylated by alkyl halides in presence of sodium ethoxide in ethanol due to their reduced acidity and to steric hindrance [2-10]. It was shown [9, 10] that this difficulty can be overcome by performing the alkylation in presence of sodium tert butoxide in tert butyl alcohol. The acidity of this solvent is lower than that of ethanol, and the corresponding alkoxide is a stronger base.

This technique was applied to the alkylation of previously synthesized esters [1] with methyl iodide. In this way satisfactory yields were obtained of methyl(α, β-dimethylpropyl)malonic, methyl(α-methylbutyl)malonic, methyl(α-phenylethyl)malonic, and methyl(α-o-tolylethyl)malonic esters.

Some chemical properties of these esters were studied. They were saponified with alcoholic potassium hydroxide, and it was found that complete saponification was not effected even after 10 hours' boiling with alcoholic alkali. The products of the reaction were mixtures of the corresponding dicarboxylic acid and its monoethyl ester.

We succeeded in separating the components of this mixture in each case and we isolated the corresponding dicarboxylic acids and their monoethyl esters. Decarboxylation of these substances led to the monocarboxylic acids and their ethyl esters. The latter were also synthesized by esterification of the corresponding monocarboxylic acids with ethyl alcohol.



These features of the reaction of hydrolysis of esters of the formula $RCH(CH_3)C(CH_3)(COOC_2H_5)_2$ are evidently a very characteristic reflection of the steric hindrances to the reaction due to blockage of the space round the reactive groups by large, branched radicals.

Most of the synthesized compounds have not been described in the literature.

EXPERIMENTAL

The initial substances for the investigation were α,β-dimethylpropylmalonic ester, α-methylbutylmalonic ester, α-phenylethylmalonic ester, and α-(o-tolyl)ethylmalonic ester, which we had synthesized earlier [1].

Preparation of esters $RCH(CH_3)C(CH_3)(COOC_2H_5)_2$. The literature method [10], with some modifications, was used for synthesis of these esters.

TABLE 1. Dialkylmalonic Esters $RCH(CH_3)C(CH_3)(COOC_2H_5)_2$*

R	Yield (in %)	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empirical formula	%C found	%C calc.	%H found	%H calc.
C_3H_7	71.3	92—93° (1.5)	0.9679	1.4327	65.44	65.54	$C_{13}H_{24}O_4$	63.93	63.93	10.10	9.84
iso-C_3H_7	75.0	100—101 (2.5)	0.9778	1.4355	65.18	65.54	$C_{13}H_{24}O_4$	63.68	63.93	9.97	9.84
C_6H_5	55.3	137—138 (2.0)	1.0601	1.4910	75.95	75.80	$C_{16}H_{22}O_4$	69.00	69.06	8.13	7.91
o-$CH_3C_6H_4$	65.0	141—142 (2.0)	1.0538	1.4940	80.67	80.41	$C_{17}H_{24}O_4$	69.66	69.86	8.33	8.22

* One of these esters [methyl(α-methylbutyl)malonic ester] has been described in the literature. It was synthesized by the action of sec amyl bromide on methylmalonic ester. The yield was poor [11].

TABLE 2. Neutralization Numbers of Products of Hydrolysis of Esters $RCH(CH_3)C(CH_3)(COOC_2H_5)_2$

R	Neutralization number found	Neutralization number calculated for dicarboxylic acid	Neutralization number calculated for monoethyl ester of dicarboxylic acid	Composition of mixture (%) dicarboxylic acid	Composition of mixture (%) monoethyl ester of dicarboxylic acid
C_3H_7	427	597	260	52.86	47.15
iso-C_3H_7	370	597	260	34.22	65.78
C_6H_5	317	506	244	35.75	64.58
o-$CH_3C_6H_4$	296	475	213	33.75	66.25

TABLE 3. Dialkylmalonic Acids $RCH(CH_3)C(CH_3)(COOH)_2$

R	Melting point	Neutralization number found	Neutralization number calculated	Empirical formula	%C found	%C calculated	%H found	%H calculated
C_3H_7	139—140°	592	597	$C_9H_{16}O_4$	57.29	57.45	8.47	8.51
iso-C_3H_7	123.5—124.5	590	597	$C_9H_{16}O_4$	57.54	57.45	8.64	8.51
C_6H_5	112—113	503	506	$C_{12}H_{14}O_4$	64.57	64.86	6.10	6.36
o-$CH_3C_6H_4$	145—146	—	—	$C_{13}H_{16}O_4$	65.92	66.10	6.59	6.78

TABLE 4. Dialkylacetic Acids $RCH(CH_3)CH(CH_3)COOH$

R	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	Neutralization number found	Neutralization number calculated	Empirical formula	%C found	%C calculated	%H found	%H calculated
C_3H_7	86—78° (1.0)	0.9199	1.4290	391	390	$C_{18}H_{16}O_2$	66.81	66.67	11.26	11.11
iso-C_3H_7	89—90 (1.5)	0.9279	1.4310	388	390	$C_{18}H_{16}O_2$	66.89	66.67	11.19	11.11
C_6H_5	M.p. 131—132 (from C_6H_6)	—	—	318	315	$C_{11}H_{14}O_2$	74.01	74.16	8.16	7.87
o-$CH_3C_6H_4$	M.p. 127—128 (from C_6H_6)	—	—	296	292	$C_{12}H_{16}O_2$	74.64	75.00	8.58	8.33

TABLE 5. Ethyl Esters of Dialkylacetic Acids $RCH(CH_3)CH(CH_3)COOC_2H_5$

R	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	Empirical formula	%C found	%C calculated	%H found	%H calculated
C_3H_7	68–69° (6.5)	0.8741	1.4193	49.72	50.03	$C_{10}H_{20}O_2$	69.96	69.77	11.72	11.63
iso-C_3H_7	65.5–65.8 (6.5)	0.8768	1.4220	49.85	50.03	$C_{10}H_{20}O_2$	69.61	69.77	11.78	11.63
C_6H_5	129–130 (10)	0.9812	1.4877	60.46	60.29	$C_{12}H_{18}O_2$	75.57	75.72	9.04	8.74
o-$CH_3C_6H_4$	109–111 (3)	0.9880	1.4939	64.81	64.91	$C_{13}H_{20}O_2$	76.24	76.36	9.25	9.09

To a mixture of 0.1 mole of monoalkylmalonic ester $RCH(CH_3)CH(COOC_2H_5)_2$ in 40 ml of 100% tert butyl alcohol, in a round-bottomed flask fitted with mechanical stirrer and reflux condenser, was added 2.35 g of finely pulverized metallic sodium. After the sodium had dissolved, 18 g of methyl iodide was slowly added to the mixture which was then boiled on an oil bath until neutral (2-3 hr). The excess of tert butyl alcohol was distilled off, and the dialkylmalonic ester formed was separated in the usual manner. The reaction product was fractionated in vacuo. The properties of the products are set forth in Table 1.

Hydrolysis of ester $RCH(CH_3)C(CH_3)(COOC_2H_5)_2$. The dialkylmalonic esters (Table 1) were hydrolyzed by heating with 15% alcoholic solution of potassium hydroxide for 4 hr; the solution was then diluted with water, the alcohol distilled off, and the residue (after acidification with sulfuric acid) extracted with ether. The ethereal extracts were dried with calcined calcium chloride and the ether carefully distilled. The residual viscous oil was found (on the basis of a study of the neutralization numbers of the products of hydrolysis [12]) to be a mixture of the corresponding dicarboxylic acids and their monoethyl esters (Table 2).

In experiments with more prolonged heating (10 hr), starting from methyl-(α,β-dimethylpropyl)malonic and methyl(α-methylbutyl)malonic esters, the reaction products were also mixtures of dicarboxylic acids and their monoethyl esters in approximately 1 : 1 ratio.

We developed a method of separation of the dicarboxylic acids from their monoethyl esters which was based on their different dissociation constants. The mixture of dicarboxylic acid and its monoethyl ester was dissolved in ether, and the solution was treated with aqueous potassium hydroxide in quantity slightly less than that theoretically needed for neutralization of the dicarboxylic acid. Since the dicarboxylic acids have a dissociation constant larger than that of the acid esters, the former went into solution in the alkali and could be extracted from the latter (after acidification) with ether; the ether was then driven off and the dicarboxylic acid purified by recrystallization from benzene.

The ethereal solution remaining after the first alkaline extraction was then treated again with aqueous alkali. This time the quantity of potassium hydroxide was slightly larger than that theoretically required for the residue of the dicarboxylic acid. In this manner the residue of dicarboxylic acid was removed. The monoethyl esters of the corresponding dicarboxylic acids were then recovered from the ethereal solution by distillation of the solvent.

By this technique we were able to obtain the dialkylmalonic acids listed in Table 3. The monoethyl esters of the dicarboxylic acids could not be isolated in the pure state due to the facility with which they underwent decarboxylation during distillation.

Decarboxylation of acids $RCH(CH_3)C(CH_3)(COOH)_2$. The dialkylmalonic acids of Table 3 were decarboxylated by heating on an oil bath at 140-160° until evolution of carbon dioxide ceased. The properties of the resulting dialkylacetic acids are set forth in Table 4.

Preparation of esters $RCH(CH_3)CH(CH_3)COOC_2H_5$. The mixtures obtained after isolation of dialkylmalonic acids by the above procedure, consisting mainly of the monoethyl esters of the corresponding dicarboxylic acids, were decarboxylated by heating on an oil bath at 140-160° until carbon dioxide evolution ceased. Decarboxylation gave the ethyl esters of the corresponding dialkylacetic acids together with a small proportion of these acids. The ethyl esters of dialkylacetic acids (Table 4) were also synthesized by esterification of the acids with ethanol in presence of sulfuric acid. The properties of the esters obtained by synthesis were compared with those of the ester

prepared by decarboxylation of the monoethyl esters of dialkylmalonic acids. The agreement between the physical constants was fully satisfactory. Characterizing data for the these esters are set forth in Table 5.

The subject of the present work was proposed by V. P. Gol'mov to whom I convey my sincere thanks.

SUMMARY

1. Alkylation of the esters $RCH(CH_3)CH(COOC_2H_5)_2$ with methyl iodide in presence of sodium tert butoxide in tert butyl alcohol gave 55-75% yields of methyl(α,β-dimethylpropyl)malonic, methyl(α-methylbutyl)malonic, methyl(α-phenylethyl)malonic, and methyl(α-o-tolylethyl)malonic esters.

2. It was shown that hydrolysis of these dialkylmalonic esters with 15% alcoholic solution of potassium hydroxide leads to formation of a mixture of the corresponding dicarboxylic acids and their monoethyl esters. The partial saponification may be accounted for by steric hindrance. The yield of dicarboxylic acid depends on the nature of the alkyl radicals, increasing with increasing complexity of structure in the sequence: $C_3H_7 > C_6H_5 >$ iso-$C_3H_7 >$ o-$C_6H_4CH_3$.

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CONDENSATION OF ALDEHYDES AND KETONES

VIII. SYNTHESIS OF 2,6-DIPHENYLISONICOTINIC ACID BASED ON THE DIKETONIC CONDENSATION OF ACETOPHENONE WITH ACETALDEHYDE

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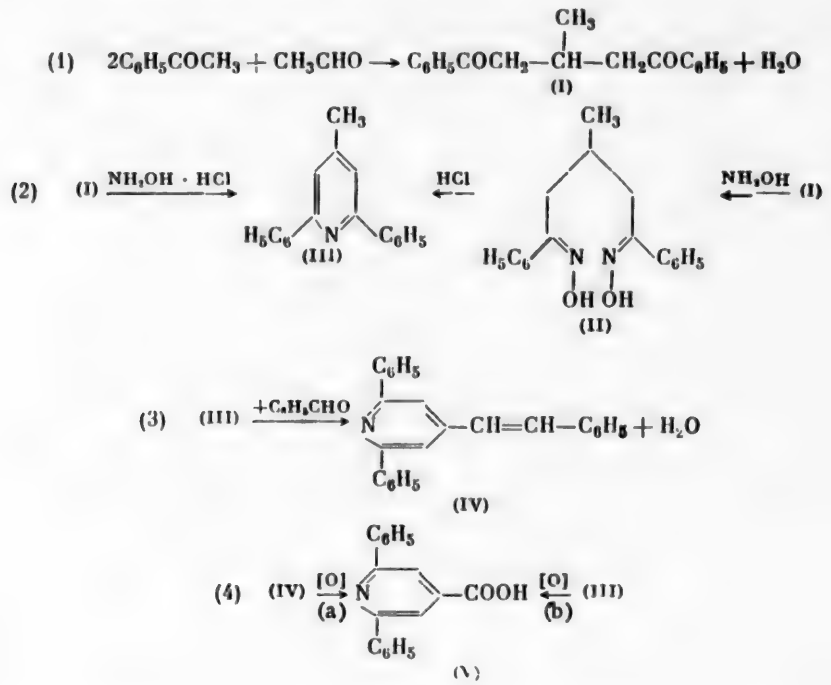
In contrast to the known [1-3] methods of synthesizing 2,6-diphenyl-4-pyridinecarboxylic (2,6-diphenylisonicotinic) acid, we accomplished the synthesis of the given compound by the scheme:



2,6-Diphenyl-4-methylpyridine (III) proved to be very stable toward oxidizing agents [4]. For this reason its direct oxidation (reaction 4b) failed to give the desired result. In only one case, and specifically, when dry potassium permanganate was added to a hot aqueous-pyridine solution of the free base were we able to obtain acid (V) in comparatively satisfactory yield (about 30%). This circumstance caused us to investigate a roundabout method (reactions 3 and 4a). In the literature [5] this method was used with success to oxidize 4-methyl-6-methoxyquinoline to quininic acid. We obtained 2,6-diphenyl-4-styrylpyridine (IV) in 86% yield, which on oxidation with permanganate in aqueous-pyridine solution gave acid (V) in 71.5% yield. The obtained acid was characterized by preparing its esters and the hydrazide. The latter was prepared for the purpose of testing its antituberculosis activity.

EXPERIMENTAL

(With the assitance of V. V. Zhukova)

The synthesis of ethylidenediacetophenone (I) and free base (III) by the above described scheme was described by us earlier [4].

2,6-Diphenyl-4-styrylpyridine. A mixture of 6 g of free base (III), 22.5 g of freshly distilled benzaldehyde and 1.5 g of anhydrous $ZnCl_2$* was heated at gentle reflux for 5 hr. The mixture after cooling was treated with 50 ml of 5 N H_2SO_4. The obtained precipitate of the sulfate of base (IV) was washed with ether, then with 60 ml of 5 N H_2SO_4, 15 ml of alcohol, and finally with 50 ml of ether. The free base was isolated by treating the salt with 80 ml of 4% aqueous NaOH solution. The yield of the base was 7 g (85.9%).

Colorless plates, m.p. 118.5-119.5° (from ligroin).

Found %: N 4.75, 4.90. M (from benzene) 334, 339. $C_{25}H_{19}N$. Calculated %: N 4.20. M 333.

2,6-Diphenylisonicotinic acid (V). a) Preparation by the oxidation of 2,6-diphenyl-4-styrylpyridine. A solution of 3.8 g of the free base in a mixture of pyridine and water (3 : 1) was cooled to 0° and then 3.8 g of $KMnO_4$ was added over 30 min; the temperature was kept below 5°. Then the mixture was held at room temperature for 2 hr. The precipitate of MnO_2 was filtered, washed with water, and the combined filtrate and wash waters was evaporated to a volume of 250 ml, followed by acidification with concentrated hydrochloric acid until acid to Congo. The thus obtained 2,6-diphenylisonicotinic acid had m.p. 278-279° (from alcohol), which corresponds to the literature data [6]. White needle crystals. Yield 2.29 g (71.5%).

Analysis of silver salt.

Found %: Ag 28.12. $C_{18}H_{12}O_2NAg$. Calculated %: Ag 28.27.

The filtrate from the separation of the 2,6-diphenylisonicotinic acid was extracted with ether to yield 0.75 g (78.2%) of benzoic acid, which after sublimination failed to depress the melting point when mixed with authentic benzoic acid.

b) Preparation by the oxidation of 2,6-diphenyl-4-methylpyridine. The given base was oxidized in the same manner as the preceding. However, oxidation at 0-5° gave the acid in only about 10% yield. Oxidation by heating on the boiling water bath for 10 hr, followed by allowing to stand for a day at room temperature, gave the acid in 29.5% yield; 67.5% of the starting base was recovered unchanged.

Methyl ester of 2,6-diphenylisonicotinic acid. The ester was prepared from 1.4 g of the silver salt of the acid by conventional treatment with methyl iodide. Colorless plates, m.p. 105.5-106.5° (from alcohol). Yield 0.92 g (87.6%).

Ethyl ester of 2,6-diphenylisonicotinic acid. Prepared by heating a mixture of 1.5 g of the acid and 0.6 ml of concentrated H_2SO_4 in 48.5 ml of anhydrous alcohol under reflux for 15 min. The mixture after cooling was poured over ice to precipitate a mixture of the acid and ester. The ester dissolved when the mixed precipitate was treated with benzene, while the acid remained in the precipitate. We extracted 0.6 g (36.3%) of the ester. Colorless rods, m.p. 98-99° (from alcohol).

Hydrazide of the acid. The hydrazide was prepared by heating an alcohol solution of the indicated esters and a 3-mole excess of hydrazine hydrate at 65-70° for 15 min. The mixture was allowed to stand overnight at room temperature. The next day the mixture was filtered, and the filtrate on evaporation deposited silky crystals of the hydrazide. Yield 78%. M.p. 179.5-180° (from alcohol).

Found %: N 14.69, 14.60. $C_{18}H_{15}ON_3$. Calculated %: N 14.53.

SUMMARY

1. Starting with acetophenone and acetaldehyde, a new method was found for the synthesis of 2,6-diphenylisonicotinic acid.

* Dry HCl gas was passed into molten $ZnCl_2$ at 360-400° for 2 hr. After this treatment the salt was used in the reaction.

2. The methyl and ethyl esters, and also the hydrazide of the indicated acid were obtained and characterized.

3. The condensation of 2,6-diphenyl-4-methylpyridine with benzaldehyde gave the previously unknown 2,6-diphenyl-4-styrylpyridine.

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SYNTHESIS OF SOME β-PHENYL-DL-ALANINE DERIVATIVES

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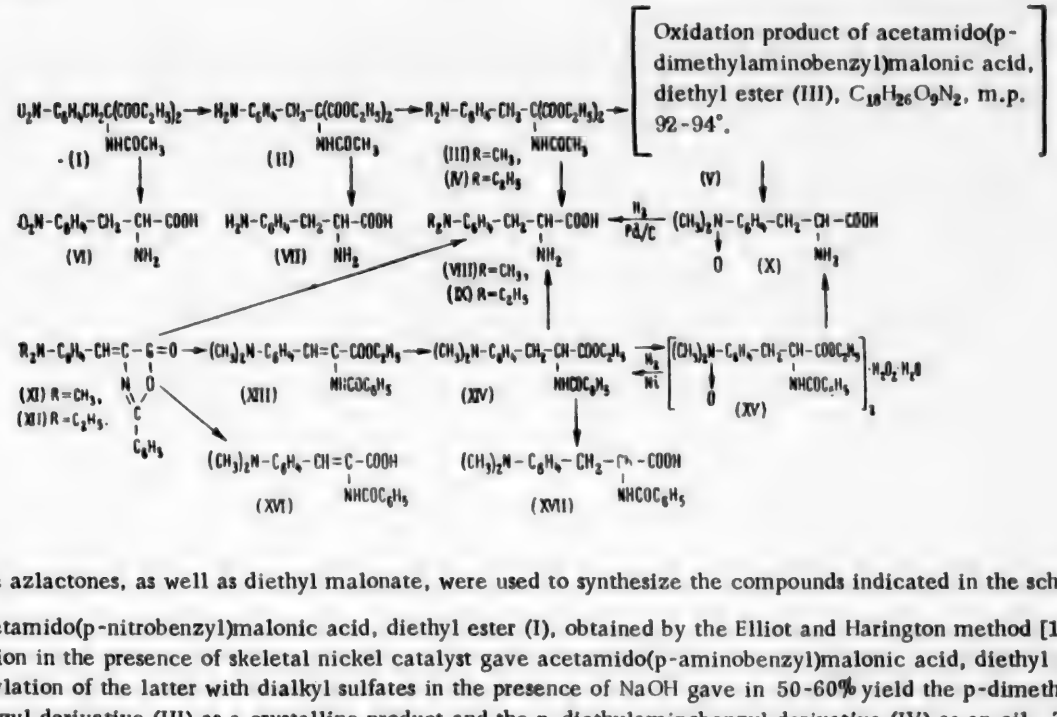
The occurrence among β-phenylalanine derivatives of biologically active compounds (sarcolysine [1], sulfur-containing analogs [2], fluoro-phenylalanines [3], etc.) aroused interest in studying derivatives of the amino acid as potential virucidal agents. The purpose of the present study was to synthesize a number of p-substituted β-phenylalanine derivatives (see scheme) for testing them on viruses. p-Dimethylaminophenylalanine N-oxide (X) and some of its derivatives (XV) were of especial interest in this respect. Both the literature data [4] and previous papers from our laboratory [5] indicate the practicality of testing these peculiar mild oxidizing agents on viruses.

p-Nitrophenylalanine (VI) was obtained earlier by many methods [6-10], p-aminophenylalanine (VII) was obtained most frequently by the reduction of p-nitrophenylalanine derivatives [6, 11], while the p-alkylaminophenylalanines have received little study. L- and D-p-dimethylamino- and L-p-diethylaminophenylalanine were obtained by the catalytic reductive alkylation of the ethyl ester of N-phthaloyl-p-nitrophenylalanine [12]. DL-p-Dimethylaminophenylalanine (VIII) was synthesized through the azlactone [13]. In the literature mention is made of the action of p-dimethylamino- (VIII) and p-diethylaminophenylalanine (IX) on the growth of the lactobacillus Leuconostos mesenteroides [14], but the method of preparation and the properties of these compounds are not given. The syntheses of N-(4-diethylamino-1-methylbutyl)-β-p-dimethylaminophenylalanine [15] and compound (XVI) [13] are also described. Compounds (III-IV, XII-XIV and XVII), and also N-oxides (V, X, XV) are not described in the literature.



The azlactones, as well as diethyl malonate, were used to synthesize the compounds indicated in the scheme.

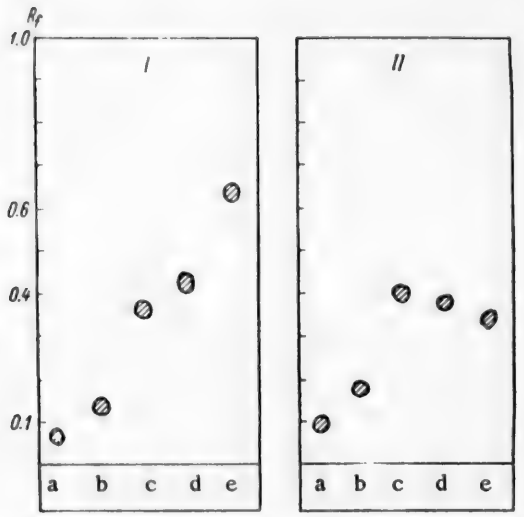
Acetamido(p-nitrobenzyl)malonic acid, diethyl ester (I), obtained by the Elliot and Harington method [16], on reduction in the presence of skeletal nickel catalyst gave acetamido(p-aminobenzyl)malonic acid, diethyl ester (II). Alkylation of the latter with dialkyl sulfates in the presence of NaOH gave in 50-60% yield the p-dimethylaminobenzyl derivative (III) as a crystalline product and the p-diethylaminobenzyl derivative (IV) as an oil. The

monoalkyl derivatives were formed along with the dialkyl derivatives, and the mixture was difficult to separate even after repeated recrystallization.

The saponification and decarboxylation of malonates (I-IV) with 6 N HCl gave the p-nitro-(VI), p-amino-(VII), p-dimethylamino-(VIII) and p-diethylamino-(IX) phenylalanines in respective yields of 76, 77, 58 and 65%. If 4-hour heating of the starting malonates (II-IV) on the boiling water bath was sufficient to obtain the p-amino- and p-dialkylaminophenylalanine derivatives (VII-IX), then in the case of the p-nitrobenzylmalonate derivative (I) complete saponification and decarboxylation was achieved only after refluxing for 25 hr.

The reaction of 1 mole of p-aminophenylalanine (VII) with 2 moles of salicylaldehyde in aqueous-alcohol solution gave α-aminosalicylidene-p-aminophenylalanine in 77% yield. The p-amino group in the phenyl ring does not react with salicylaldehyde under these conditions.

p-Dimethylamino- (VIII) and p-diethylaminophenylalanine (IX) were also obtained by a second method, through the azlactones, which were synthesized by the Erlenmeyer method from hippuric acid and the appropriate aldehydes. The azlactone of α-benzamido-p-diethylaminocinnamic acid (XII) was obtained in 67% yield. Treatment of the azlactones with hydriodic acid in the presence of red phosphorus and acetic anhydride gave p-dimethylamino- (VIII) and p-diethylaminophenylalanine (IX) in respective yields of 73 and 44%. The acid hydrolysis of azlactone (XI) gave α-benzamido-p-dimethylaminocinnamic acid (XVI) in 90% yield. In obtaining the ethyl ester of α-benzamido-p-dimethylaminocinnamic acid (XIII) by the alcoholysis of azlactone (XI) it was observed that acid alcoholysis leads to the formation of a mixture of the two geometric isomers of unsaturated ester (XIII), melting in the range 137-160°. The alkaline alcoholysis of azlactone (XI) led to the formation, in quantitative yield, of only one isomer of (XIII), with m.p. 138-139°.



Chromatograms of p-substituted phenylalanine derivatives when developed with various solvents: a) p-dimethylaminophenylalanine N-oxide; b) p-amino-; c) p-nitro-; d) p-dimethylamino-; and e) p-diethylaminophenylalanine. Developing solvent: I) Butanol-propanol−0.1 N NH_4OH (2 : 1 : 1); II) butanol − propanol−0.1 N CH_3COOH (2 : 1 : 1).

The catalytic hydrogenation of the obtained unsaturated ester (XIII) in the presence of skeletal nickel at room temperature in anhydrous alcohol gave the ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XIV) in quantitative yield.

Saponification of the obtained ester (XIV) by refluxing it for 10 hr with excess sodium carbonate solution gave the sodium salt of α-benzyl-p-dimethylaminophenylalanine in 93% yield. α-Benzoyl-p-dimethylaminophenylalanine (XVII) crystallized out when the sodium salt was neutralized with an equivalent amount of hydrochloric acid, followed by evaporation of the solution. Attempts to obtain the same compound by the catalytic hydrogenation of the corresponding unsaturated acid (XVI) in anhydrous ethanol in the presence of skeletal nickel proved unsuccessful.

p-Dimethylaminophenylalanine (VIII) was obtained in 83% yield when ester (XIV) was heated with 6 N HCl solution for 4 hr on the boiling water bath. This product was identical with the p-dimethylaminophenylalanine obtained by the two methods described above.

The oxidation of compounds (III) and (XIV) with peracids and hydrogen peroxide in glacial acetic acid and acetic anhydride, made for the purpose of obtaining the N-oxides, failed to yield any definite results. Only when the oxidation was run with a large excess of hydrogen peroxide at 60-70° in aqueous solution did compounds (III) and (XIV), insoluble in water, go completely into solution in 30-40 hr. Viscous oily liquids were obtained after removal of the water and excess hydrogen peroxide by vacuum-distillation, which on standing in a vacuum-desiccator solidified to colorless hydroscopic substances (V) and (XV), insoluble in ether. The latter were purified by repeated reprecipitation with absolute ether from ethanol solution. Both substances liberate iodine from sodium iodide in neutral solution.

The elemental composition of both compounds indicates that they are not the pure N-oxides, but instead they contain an excess of oxygen. A more detailed study was made of the substance obtained from (XIV). Both the permanganate and iodometric titration of this compound revealed that it contained 0.5 mole of hydrogen peroxide. Catalytic reduction of the material in anhydrous ethanol in the presence of skeletal nickel led to the isolation of the ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XIV), which indicates that the molecular structure of (XIV) is retained when the compound is oxidized with hydrogen peroxide under the above described conditions. This data, the elemental analysis results, and determination of the amount of water, made it possible to assume that the product isolated by us from the oxidation of ester (XIV) is the monohydrate of the addition product of 1 mole of hydrogen peroxide to 2 moles of the N-oxide of the ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XV). The structure of compound (V) was not investigated.

When the hydrolyzates, obtained by heating compounds (V) and (XV) with excess 6 N HCl solution on the boiling water bath for 3 hr, were chromatographed on paper we discovered in both cases only one stain that gave a positive ninhydrin test. This stain had R_f 0.05 and belonged to the N-oxide of p-dimethylaminophenylalanine (X). Since the hydrochloride of the N-oxide, isolated from the hydrolyzates of compounds (V) and (XV) by the removal of water and hydrochloric acid, is extremely hygroscopic and could not be recrystallized, then to purify it, the compound was precipitated from ethanol solution using absolute ether, after which the hydrochloride was converted to the free base by shaking its aqueous solution with anionite EDE-10P. After precipitation from ethanol solution with ether, the free base obtained in this manner was recrystallized from a mixture of 90% aqueous ethanol and ether. From compounds (V) and (XV) we obtained in 20-25% yield a colorless crystalline substance with m.p. 192° (decomp.) and R_f 0.05, representing the N-oxide of p-dimethylaminophenylalanine (X). The structure of this substance (in addition to the elemental analysis data) was confirmed by the fact that p-dimethylaminophenylalanine is formed when the compound is reduced with hydrogen in the presence of skeletal nickel or 5% Pd-on-carbon. Reduction of the N-oxide group with the formation of p-dimethylaminophenylalanine also occurs on long standing of aqueous solutions of the N-oxide in the light, which is manifested by the appearance on the chromatogram of a second stain, giving a positive ninhydrin test. This stain has R_f 0.43 and corresponds to p-dimethylaminophenylalanine.

It is known that when the pH of the aqueous phase is reduced in the chromatographing of amino acids on paper the character of the changes in the R_f values of amino acids depends on the nature of the latter: for monobasic diamino acids the R_f value decreases, while for dibasic monoamino acids it increases. Similar to this, the p-dialkylaminophenylalanines (VIII) and (IX) move at a slower rate in the presence of CH_3COOH than in the presence of NH_4OH, while p-nitrophenylalanine (VI), in contrast, moves at a more rapid rate (Figure). Oxidized p-dimethylaminophenylalanine (X) behaves in the same manner as p-nitrophenylalanine, which confirms the presence of the N-oxide group in compound (X).

The obtaining of p-dimethylaminophenylalanine N-oxide expands the concepts relating to the action of hydrogen peroxide on amino acids with a substituted amino group and makes it possible to pass over to the synthesis of peptides, containing p-dialkylaminophenylalanine N-oxide.

The results of the biological testing of the synthesized compounds will be published separately.

EXPERIMENTAL*

Preparation of p-Alkylaminophenylalanine Derivatives Via the Malonates

p-Nitrophenylalanine hydrochloride (VI). With vigorous stirring, a mixture of 1.0 g of compound (I) and 25 ml of 6 N HCl was refluxed for 25 hr. We obtained 0.53 g of crystalline hydrochloride (VI) with m.p. 230° (began to decompose at 214°). Yield 76%.

Found %: N 11.32. $C_9H_{10}O_4N_2 \cdot HCl$. Calculated %: N 11.35.

Employing the technique of ascending paper chromatography,** we detected one stain that gave a positive ninhydrin test and had R_f 0.37.

* All of the melting point determinations of the free amino acids were taken in sealed capillaries, inserted in the apparatus previously heated to 170-180°.

** Here and in all of the other cases the chromatographing was done on Leningrad paper "Chromatographic Rapid" in an ascending stream of the developing solution of composition: butanol–propanol–0.1 N aqueous ammonia (2 : 1 : 1).

From the hydrochloride we isolated the free base with m.p. 240-243° (decompn.). According to the literature [6], m.p. 240-245°.

p-Aminophenylalanine (VII) was obtained in 77% yield and had m.p. 248-250° (decompn.), which corresponds to the literature data [16]. One stain was detected when the compound was chromatographed on paper. This stain gave a positive ninhydrin test and had R_f 0.14. Bergel and Stock erroneously give R_f 0.53 for (VII). Actually, this is obviously the R_f value for unreacted p-nitrophenylalanine [12].

α-Aminosalicylidene-p-aminophenylalanine. A solution of 1.086 g of salicylaldehyde in 20 ml of alcohol was added in drops to a hot solution of 0.8 g of p-aminophenylalanine (VII) in a mixture of 15 ml of H_2O and 80 ml of alcohol. The mixture was heated under reflux at 70-80° for 40 min. The obtained yellow precipitate was separated and washed with alcohol. We obtained 0.97 g (77 %) of the azomethine with m.p. 218-219° (decompn.). The ninhydrin reaction was negative. The substance proved to be insoluble in most organic solvents. It was soluble in hot benzyl alcohol or formamide.

Found %: C 67.36, 67.42; H 5.60, 5.10; N 9.60, 9.79. $C_{16}H_{16}O_3N_2$. Calculated %: C 67.60; H 5.66; N 9.84.

Diethyl acetamido(p-dimethylaminobenzyl)malonate (III). A solution of 4.0 g of compound (II) in 20 ml of acetone was treated with 2.3 ml of dimethyl sulfate and 2.5 ml of 40% aqueous NaOH solution. The mixture was shaken vigorously for 2 hr. The acetone was distilled from the upper layer, and the residue was recrystallized from ethanol, yielding 2.73 g (63%) of a colorless crystalline substance (III), melting after 4 recrystallizations from 50% ethanol at 124-126°; the compound was obtained as microscopic plates.

Found %: C 61.31, 61.82; H 7.47, 7.53; N 8.11, 8.50. $C_{18}H_{26}O_5N_2$. Calculated %: C 61.71; H 7.43; N 8.00.

The picrate is formed in aqueous-alcohol solution, m.p. 157-158°.

Dilution of the mother liquor from the synthesis of compound (III) with water led to the deposition to a yellow substance with m.p. 152-153° (from aqueous alcohol). The chromatographing on paper of the hydrolyzates of the products with m.p. 124-126° and 152-153° (6 N HCl, heating for 4 hr on the boiling water bath) revealed that the substance with m.p. 124-126° forms three stains that give a positive ninhydrin test. These three stains have R_f 0.43 (principal stain, corresponding to p-dimethylaminophenylalanine), 0.31 (weakly colored stain, apparently p-monomethylaminophenylalanine), and 0.15 (hardly noticeable stain of p-aminophenylalanine). The substance with m.p. 152-153° forms two stains that give a positive ninhydrin test. These two stains have R_f 0.31 (principal stain) and 0.15 (weakly colored). These data testify to the insufficient purity of the product with m.p. 124-126°.

p-Dimethylaminophenylalanine (VIII). A mixture of 0.4 g of compound (III) and 4 ml of 6 N HCl was heated on the boiling water bath for 4 hr. The hydrochloric acid solution was evaporated to a small volume, diluted with water, and then evaporated again. The residue was neutralized with concentrated ammonia to pH 6.5. The colorless precipitate of p-dimethylaminophenylalanine (0.14 g, 58%), after recrystallization from water, melted with decomposition at 256°. From the literature [13], m.p. 256-258°. Only one stain, giving a positive ninhydrin test and having R_f 0.43, was obtained when the compound was chromatographed on paper.

Found %: N 13.39. $C_{11}H_{16}O_2N_2$. Calculated %: N 13.46.

Diethyl acetamido(p-diethylaminobenzyl)malonate (IV) was obtained in the same manner as the p-dimethylaminomalonate (III). It represented a viscous oil that could not be made to crystallize. Yield 50-60%.

p-Diethylaminophenylalanine (IX) was obtained in the same manner as p-dimethylaminophenylalanine (VIII) from malonate (IV) in 65% yield. It represented a colorless amorphous substance with m.p. 207-210° (decompn.). The compound could not be purified by recrystallization from aqueous alcohol, and consequently the elemental analysis results were unsatisfactory. However, despite the low melting point (see below), the substance when chromatographed on paper gives but a single stain that shows a positive ninhydrin test. This stain has R_f 0.63, which coincides with the R_f for the p-diethylaminophenylalanine that we obtained through the azlactones.

Preparation of p-Alkylaminophenylalanine Derivatives Through the Azlactones

α-Benzamido-p-dimethylaminocinnamic acid (XVI) was obtained in 90% yield and had m.p. 214-216° (from alcohol). From the literature [13], m.p. 225-226°.

Found %: C 69.85, 69.78; H 5.93, 5.95. $C_{18}H_{18}O_3N_2$. Calculated %: C 69.66; H 5.81.

Ethyl ester of α-benzamido-p-dimethylaminocinnamic acid (XIII). a) A solution of 8.0 g of azlactone (XI) in 56 ml of anhydrous ethanol was heated in the presence of 4.0 ml of concentrated H_2SO_4 on the boiling water bath for 1 hr. After cooling, the solution was poured into 400 ml of water and neutralized with dilute NaOH solution to pH 7.5. The obtained yellow-brown tar was recrystallized from 50% aqueous ethanol to give 3.5 g (38% yield) of a yellow substance with m.p. 147-160°. The substance decolorizes $KMnO_4$ in acetic acid solution.

Found %: C 70.77, 71.08; H 6.82, 6.46. $C_{20}H_{22}O_3N_2$. Calculated %: C 71.00; H 6.51.

A solution of 1.8 g of the substance with m.p. 147-160° in 20 ml of ethyl acetate was cooled to -15° to yield 0.28 g of a substance with m.p. 155-164°, while evaporation of the mother liquor gave 1.3 g of a substance with m.p. 135-143°. Both substances decolorize $KMnO_4$ in acetic acid solution.

Found %: N 8.16 (substance with m.p. 135-143°), 8.01 (substance with m.p. 155-164°). $C_{20}H_{22}O_3N_2$. Calculated %: N 8.28.

Hydrogenation of the substances in anhydrous alcohol in the presence of skeletal nickel gave in both cases the ethyl ester of α-benzamido-p-dimethylaminophenylalanine (XIV) in 80% yield.

b) A solution of 1.0 g of azlactone (XI) in 30 ml of boiling anhydrous alcohol, containing 0.02 g of NaOH, was refluxed for 5 min and then the hot solution was poured into 200 ml of water. On cooling we obtained 1.14 g (98%) of a pinkish-yellow substance with m.p. 138-139° (from alcohol).

Found %: N 8.28, 8.26. $C_{20}H_{22}O_3N_2$. Calculated %: N 8.28.

Ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XIV). A solution of 5.4 g of unsaturated ester (XIII) in 200 ml of anhydrous alcohol was hydrogenated in the presence of 6 g of skeletal nickel at 18° and 70 cm of water pressure. The hydrogenation was ended in 4 hr. The catalyst was filtered, and the alcohol was vacuum-distilled. From the residue we isolated 5.3 g (98%) of saturated ester (XIV) with m.p. 107-110°. After recrystallization from 60% ethanol, m.p. 110-111° (needles).

Found %: C 70.75, 71.14; H 7.15, 7.24; N 8.23. $C_{20}H_{24}O_3N_2$. Calculated %: C 70.60; H 7.13; N 8.24.

The picrate with m.p. 171° (from alcohol) was obtained as prisms when alcohol solutions of ester (XIV) and picric acid were poured together.

α-Benzoyl-p-dimethylaminophenylanine (XVII). Two grams of ester (XIV) was refluxed with 2.0 g of sodium carbonate in 20 ml of water for 10 hr. Then the sodium carbonate was precipitated by the addition of 5 volumes of alcohol, separated by filtration, and the filtrate was evaporated in vacuo to dryness. The residue, after recrystallization from anhydrous alcohol, gave 1.8 g (100%) of the Na salt of α-benzoyl-p-dimethylaminophenylalanine with m.p. 267° (needles, collecting into handsome clumps). A solution of 0.5 g of the salt in 15.5 ml of 0.1 N HCl, after partial evaporation, gave 0.4 g of the acid (XVII) with m.p. 179-180° (from water).

Found %: N 8.48. $C_{18}H_{20}O_3N_2 \cdot H_2O$. Calculated %: N 8.48.

p-Dimethylaminophenylalanine (VIII). a) The compound was obtained in 73% yield by the saponification and reduction of the azlactone [13] (XI); m.p. 256° (decompn., from water).

Found %: N 13.76. $C_{11}H_{16}O_2N_2$. Calculated %: N 13.46.

b) A mixture of 1.0 g of the ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XIV) and 10 ml of 6 N HCl was heated for 4 hr on the boiling water bath. Then the solution was cooled, the benzoic acid was filtered, and any residual acid was extracted with ether. The solution, after removal of excess HCl by evaporation in vacuo, was heated and then saturated with gaseous ammonia to pH 6.5. We obtained 0.51 g (83%) of compound (VIII) with m.p. 256° (decompn., from water). In both cases only one stain, giving a positive ninhydrin test and having R_f 0.43, was obtained when the amino acid was chromatographed on paper.

Azlactone of α-benzamido-p-diethylaminocinnamic acid (XII). A mixture of 16.0 g of p-diethylaminobenzaldehyde [17], 16.2 g of hippuric acid, 7.3 g of anhydrous sodium acetate and 27 ml of acetic anhydride was mixed well and then heated for 20 min at a bath temperature of 110-115°. The red melt was cooled, triturated with ice water, and then washed with alcohol and ether. We obtained 19.5 g (67.5%) of the azlactone (XII) as red prisms with m.p. 134-135° (from alcohol).

Found %: N 8.80. $C_{20}H_{20}O_2N_2$. Calculated %: N 8.75.

p-Diethylaminophenylalanine (IX). A mixture of 6.0 g of azlactone (XII), 6.0 g of red phosphorus, 30 ml of acetic anhydride and 30 ml of freshly distilled hydriodic acid was refluxed for 1.5 hr. The mixture was then cooled, carefully filtered from the phosphorus, and the filtrate was evaporated in vacuo to dryness. The residue was suspended in cold water, filtered from the benzoic acid, and then boiled with activated carbon. The filtrate was heated and neutralized with concentrated aqueous ammonia to pH 6.5. The obtained precipitate was recrystallized from 30% aqueous ethanol, yielding 1.95 g (44.1%) of p-diethylaminophenylalanine with a constant m.p. of 243° (decompn.). Only one stain, giving a positive ninhydrin test and having R_f 0.63, was detected when the substance was chromatographed on paper. The substance was dried at 100° (20 mm) for 2 hr.

Found %: C 64.82, 65.18; H 8.32, 8.38; N 11.43, 11.48. $C_{13}H_{20}O_3N_2 \cdot {}^1/_3H_2O$. Calculated %: C 64.44; H 8.62; N 11.56.

Oxidation of ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XIV). A suspension of 0.5 g of ester (XIV) in 5 ml of water and 0.35 ml of 30% H_2O_2 was stirred at 60-70°, and then 0.3 ml portions of 30% H_2O_2 were added at 6 hr intervals. After 30 hr, ester (XIV) had dissolved completely. Evaporation of the solution in vacuo to dryness left 0.53 g of a colorless frothy mass. When this mass was washed with ether, followed by drying in a vacuum-desiccator, we obtained 0.53 g of a colorless hygroscopic substance, readily soluble in alcohol, and insoluble in ether. The substance had m.p. 58-60°, and foamed strongly on further heating, darkening at 150°. The substance liberates iodine from neutral aqueous NaI solution and decolorizes $KMnO_4$ solution. After four consecutive reprecipitations from alcohol solution with ether, followed by drying in a vacuum-desiccator, the properties and composition of the substance remained constant.

Found %: C 62.82, 62.98, 62.78; H 6.68, 6.47, 6.64; N 7.55. $C_{40}H_{48}O_9N_4 \cdot 2H_2O$. Calculated %: C 62.70; H 6.96; N 7.32.

Picrate, m.p. 130-132° (decompn., from alcohol).

To determine the amount of moisture, the substance was heated for 6 hr in a vacuum-pistol (steam-heated). Here a yellowing was observed. The dried substance does not liberate iodine from neutral and acid NaI solution. M.p. 130-135° (decompn.).

Found %: H_2O 4.2. $C_{40}H_{48}O_9N_4 \cdot 2H_2O$. Calculated %: H_2O 4.7.

The hydrogen peroxide was determined iodometrically in aqueous acetic acid solution (found: 5.08% H_2O_2) and using permanganate in 5% H_2SO_4 (found: 5.3% H_2O_2). A sample of the substance, after standing for 6 months in a vacuum-desiccator in the light, was analyzed by the permanganate method and found to contain 5.1% H_2O_2.

A solution of 1.14 g of the substance in 150 ml of anhydrous alcohol was subjected to catalytic reduction in the presence of 4 g of skeletal nickel for 8 hr. The filtrate from the separation of the catalyst was evaporated in vacuo to dryness. From the residue we isolated 0.8 g of substance with m.p. 105-107°. After recrystallization from alcohol, m.p. 110-111°. The melting point was not depressed when the substance was mixed with (XIV).

Oxidation of diethyl acetamido(p-dimethylaminobenzyl)malonate (III). A suspension of 0.9 g of malonate (III) in 6 ml of water and 5 ml of 30% H_2O_2 was stirred for 6 hr at 60-70°, after which another 3 ml of H_2O_2 was added. After 25-30 hr the undissolved precipitate was filtered (0.2 g with m.p. 157-160°). The filtrate was evaporated in vacuo to dryness. The oily residue was washed twice with ether, precipitated from alcohol solution with ether, and solidified when kept in a vacuum-desiccator, yielding 0.66 g (70%) of colorless substance with m.p. 92-94° (decompn.). The substance liberates iodine from neutral aqueous NaI solution. The substance was purified by reprecipitating 5 times from alcohol solution with ether.

Found %: C 52.27, 52.60; H 6.33, 6.26; N 6.92, 71. $C_{18}H_{26}O_9N_2$. Calculated %: C 52.20; H 6.28; N 6.76.

The picrate was obtained by mixing water solutions of the substance and picric acid. M.p. 144-145° (decompn.).

p-Dimethylaminophenylalanine N-oxide (X). a) A mixture of 1.5 g of the oxidized ethyl ester of α-benzoyl-p-dimethylaminophenylalanine (XV) and 20 ml of 6 N HCl was heated for 4 hr on the boiling water bath. After removal of the benzoic acid, the hydrolyzate was evaporated in vacuo to dryness, after which the residue was dissolved in water and again evaporated to dryness. The yellow residue of the hydrochloride was dissolved in 25 ml of water and then shaken with anionite EDE-10P to pH 6.0. The filtrate was evaporated in vacuo to dryness, and the residue was reprecipitated from alcohol solution with ether, followed by recrystallization from 90% aqueous alcohol,

with the addition of ether to incipient cloudiness. We obtained 0.2 g (23.5%) of a colorless crystalline substance as plates with m.p. 192° (decompn., when heated in an open capillary). When heated in a sealed capillary the substance melts at 210-211° (decompn.). Only one stain, giving a positive ninhydrin test and having R_f 0.05, was detected when the substance was chromatographed on paper, using a solvent with the composition: butanol–propanol–0.1 N aqueous ammonia (2 : 1 : 1). When the ammonia in the solvent is replaced by acetic acid the R_f value increases to 0.09. A second stain, giving a positive ninhydrin test and having R_f 0.43, was obtained when a water solution of the substance was allowed to stand in the light for 20 days.

Found %: C 58.63; H 7.35; N 12.62. $C_{11}H_{16}O_3N_2$. Calculated %: C 58.90; H 7.20; N 12.50.

b) A mixture of 0.8 g of oxidized diethyl acetamido(p-dimethylaminobenzyl)malonate (V) and 10 ml of 3 N HCl was heated for 3 hr on the boiling water bath and then was worked up in the same manner as the preceding substance. We obtained 0.1 g (23%) of the N-oxide (X) with m.p. 192° and R_f 0.05. The mixed melting point with the substance obtained by the above indicated method was not depressed.

A solution of 0.05 g of substance (X) in 20 ml of methanol was hydrogenated for 2 hr in the presence of 0.5 g of 5% Pd-on-carbon at room temperature and a water pressure of 70 cm. Then 10 ml of water was added and the mixture was shaken for another hour. The filtrate was evaporated to dryness. The crude residue, melting in the range 230-260° (decompn.), gave when chromatographed on paper two ninhydrin-positive stains: the principal stain with R_f 0.43 (p-dimethylaminophenylalanine) and a weak stain with R_f 0.23 (apparently, the intermediate reduction product of the N-oxide). The same results were obtained when the N-oxide was reduced in the presence of skeletal nickel.

SUMMARY

1. p-Dimethylaminophenylalanine N-oxide was synthesized and its structure was proved.

2. It was shown that it is possible to obtain p-dialkylaminophenylalanines by the alkylation of diethyl acetamido(p-aminobenzyl)-malonate with alkyl sulfates.

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REACTION OF 1-HALOANTHRAQUINONE WITH PRIMARY AROMATIC AMINES IN AHYDROUS MEDIUM

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In the anthraquinone series the replacement of halogen by an arylamino group is one of the most widely known reactions. The aramination of 1-haloanthraquinones, as a rule, occurs only in the presence of catalysts—copper or copper compounds, i.e., it represents a partial case of the Ullmann reaction. The process goes more smoothly and vigorously in the presence of alkaline agents [1].

The information in the literature pertaining to the course of this reaction is very limited. In a review of nucleophilic substitutions [2], Bunnett places all Ullmann reactions in the group of processes with an unknown mechanism. According to the investigations of N. N. Vorozhtsov and coworkers [3], the replacement of aromatically bound halogen by an amino group in aqueous medium, in the presence of copper compounds, proceeds through the intermediate compound, $[ArCl \cdot Cu(NH_3)_2]^+$. Groggins [4] also indicates that it is possible to form the intermediate ternary complex in this reaction. L. Kh. Freidlin and A. A. Balandin with coworkers [5] characterize copper and its compounds as a catalyst that "loosens" the C—Hal bond and "prepares the haloaryl for any reaction," which, apparently, may be the reason for several concurrent processes taking place in the reaction sphere. Mention should also be made of the theory of Waters [6] that the Ullmann reaction in the presence of copper compounds has a free radical course.

In the present paper a study was made of the replacement of halogen in the anthraquinone series by an arylamino group in anhydrous medium in the presence of potassium acetate and copper. In preliminary experiments we became convinced that at 95-98° the aramination of 1-chloro- and 1-bromoanthraquinone is mainly a catalytic reaction. Thus, when 1-bromoanthraquinone was heated in excess aniline at this temperature for 12 hr, in the absence or in the presence of potassium acetate, the amount of cleaved halogen was respectively 4 and 7%. In the presence of 5 mole % of metallic copper and potassium acetate, under the same conditions, the reaction went to the extent of 95-96% in 2 hr. It is interesting to mention that in the presence of copper, but omitting the acetate, the aramination did not go smoothly and only to the extent of 20-25%.

We first attempted to follow the changes taking place in the copper catalyst during the aramination process. It is known that many copper salts form complexes with primary aromatic and aliphatic amines [7, 8]. It proved that not all copper compounds, exhibiting catalytic activity in the aramination process, react with aniline to form a complex. Of the bivalent copper compounds investigated by us, $CuSO_4$, $CuCl_2$, $CuBr_2$ and $Cu(CH_3COO)_2$ readily form complexes with aniline, but all of the attempts made to obtain the complexes of aniline with $Cu(OH)_2$ and $CuCO_3 \cdot Cu(OH)_2$ proved unsuccessful. The introduction of copper compounds as the finished complexes with aniline was without effect on the aramination results.

We were unable to find any studies in the literature on the relationship between the catalytic activity of copper compounds in the aramination reaction and the anion of the compounds. Still, this question has importance both in selecting the catalyst and for elucidation of the reaction mechanism. In Table 1 we have given the results obtained in the aramination of 1-chloro- and 1-bromoanthraquinone with aniline at 95-98° in the presence of an equimolar amount of potassium acetate. The reaction conditions for the chloro compound were a reaction time of 3 hr and using 10 mole % of various copper compounds, while for the bromo compound the conditions were a reaction time of 1 hr and 5 mole % of the copper compound.

The data in Table 1 confirm the greater catalytic activity shown by Cu^+ compounds when compared with the corresponding Cu^{++} compounds, mentioned in the literature for similar reactions [3, 9]. But, in addition to this, it

TABLE 1

Copper compound	Aramination of 1-chloroanthraquinone (in %)		Aramination of 1-bromoanthraquinone	
	amount of Cl cleaved (in % of theory)	Amt. 1-chloroanthraquinone recov. (%)	amount of Br cleaved (in% of theory)	Amt. 1-chloroanthraquinone recov. (%)
$CuSO_4$	21.15	80.6	54.36	38.0
$CuCl_2$	34.80	69.4	82.00	Traces
$CuBr_2$	40.60	38.5	68.70	19.5
$Cu(CH_3COO)_2$	42.30	57.3	87.60	2.0
$CuCO_3 \cdot Cu(OH)$	45.60	52.7		
$Cu(OH)_2$	56.76	46.7	86.70	None
CuCl	50.80	45.4		
CuBr	49.15	50.3		
CuI	5.15	90.0		
Cu_2O	7.00	89.0		
Cu	50.50	52.1		

is obvious that in anhydrous medium the nature of the anion exerts a greater effect on the catalytic activity than does the valence of the copper. It may be assumed that such an effect is the result of the copper compound, not dissociating in anhydrous medium, taking part in the formation, according to N. N. Vorozhtsov, of the intermediate compound ArCl · CuX.

Increasing the amount of catalyst increases the aramination rate, but at the same time an acceleration of the side dehalogenation reaction is observed.

In Table 2 we have given the results obtained in the aramination of 1-chloroanthraquinone with aniline in the presence of copper acetate for 2 hr at 95-98°.

We observed that the copper catalyst shows interesting transformations and properties in the absence of alkaline agents. Thus, it was found that when the complex $2Cu(CH_3COO)_2 \cdot 3C_6H_5NH_2$ (I) in aniline solution is reacted with an equimolar amount of either the hydrobromide or hydrochloride of aniline at 96-98° the hydrogen halide displaces the acetic acid moiety from the complex. The acetic acid, along with 70-80% of the aniline, may be isolated by vacuum-distillation (12 mm, 70-75°). The complexes (II and III) that are isolated from the remaining aniline contain respectively 25% Br and 14% Cl. Under analogous conditions the complex $CuSO_4 \cdot 2C_6H_5NH_2$ (IV) adds halogen in very small amounts. The same picture is observed when the aramination is run in the presence of complexes (I) and (IV) without the addition of acid-binding agents. If on conclusion of the aramination of 1-bromoanthraquinone in the presence of (I) the reaction mass is diluted with benzene, then the isolated complex contains 15-16% bromine, while the reaction mass has the sharp odor of acetic acid. The complex isolated under the same conditions after the aramination of 1-bromoanthraquinone in the presence of (IV) contains only traces of halogen. The catalytic activity of the complex after the addition of hydrogen halide to it decreases sharply in the absence of potassium acetate. If in 2 hr the aramination of 1-bromoanthraquinone with aniline in the presence of an equimolar amount of (I) went to completion, then under the same conditions with the same amount of copper, introduced as the complex (II), the reaction went to the extent of 49%.

Earlier [10], in the aramination of 1-haloanthraquinone, we had observed a side dehalogenation reaction. Now we had to contend with the presence of additional secondary products in the reaction mixture. The use of bivalent copper salts in the aramination reaction is associated with the oxidation of the aniline to azobenzene, which we were able to show by steam distillation and the fact that the mixed melting point with the authentic substance was not depressed. The amount of azobenzene formed was 0.1 mole per mole of copper acetate when the reaction mixture was heated in excess aniline for 2 hr on the boiling water bath.

In addition, we observed that the 1-anilinoanthraquinone obtained in the aramination of 1-bromoanthraquinone in anhydrous medium, after removal of the strating haloanthraquinone and any copper compounds, always contains as impurity a compound containing covalently bound bromine. The amount of this covalently bound bromine represents 10-12% of the total amount of halogen taken for reaction. We were able to show that the com-

TABLE 2

Amount of copper acetate (in mole %)	Amount of halogen cleaved (in %)	Amount of anthraquinone isolated (in %)
5 •	5.5	None
10 •	24.4	None
20 •	69.0	Traces
40	84.0	3.0
50	91.0	13.4
60	98.3	Not determined
80	98.1	17.2

• Starting 1-chloroanthraquinone was recovered.

plex of copper salt and aniline, containing bromine, possesses bromination properties. Thus, when equimolar amounts of 1-anilinoanthraquinone and $CuBr_2 \cdot C_6H_5NH_2$ were heated in toluene for 2 hr at 98°, followed by chromatographic separation from the copper compounds, the anilinoanthraquinone was found to contain 17% of the total amount of halogen taken. A more detailed study of the halogenation reaction in the synthesis of arylaminoanthraquinones is the subject of our next paper.

EXPERIMENTAL

Aramination of 1-haloanthraquinone with aniline. A mixture of 2.43 g of 1-chloroanthraquinone, 1 g of anhydrous potassium acetate and 30 ml of aniline was heated under reflux to 95°, with stirring in a gentle nitrogen stream. Then 10 mole % of anhydrous copper compound was added and the reaction mass was stirred for 3 hr at 95-98°. After this the hot mass was transferred to a steam-distillation flask and the amine was steam-distilled. The water suspension remaining in the flask was filtered and the precipitate was washed with water until free of halogen. The filtrate and wash waters were made up to 500 ml with distilled water in a volumetric flask and the amount of cleaved halogen was determined by Volhard titration.

The precipitate contained 1-anilinoanthraquinone, unreacted 1-chloroanthraquinone and 2-4% of a black deposit difficulty soluble in chloroform (apparently, the decomposition product of the copper-aniline complex). This black deposit contained copper, a small amount of nitrogen, and from 0.5 to 1.5% of the total amount of halogen.

TABLE 3

Complex	Halogen (in %)	Aniline (in %)	Cu (in %)	CH_3COO^- (by difference) (in %)
(I)	None	38.6	20.15	36.8
(II)	14 (Cl)	56.0	19.00	11.0
(III)	25 (Br)	41.4	21.85	11.75

Separation of mixture of 1-haloanthraquinone and 1-anilinoanthraquinone. Two grams of mixed 1-haloanthraquinone and 1-anilinoanthraquinone was gradually added at 20-25°, with stirring, to 25 g of 92-96% sulfuric acid. When all of the precipitate had dissolved, 50% aqueous sulfuric acid solution was added from a dropping funnel, in 1-2 hr, with vigorous stirring, in an amount sufficient to reduce the concentration of the acid in the mixture to 78-80%. Here the haloanthraquinone deposited as grayish prisms. After several hours the precipitate was filtered on a tared Schott filter, washed twice with a small amount of 70% sulfuric acid, pressed, washed with water on the funnel, then stirred with a large amount of water, filtered through the same funnel, and finally the precipitate of 1-haloanthraquinone was washed with water until neutral and then dried to constant weight.

From an artificial mixture of 1-bromoanthraquinone and 1-anilinoanthraquinone (1 : 1 by weight) we were able with such a procedure to isolate 95-96% of 1-bromoanthraquinone with m.p. 187-189°, while from a comparable mixture of 1-chloroanthraquinone and 1-anilinoanthraquinone we were able to isolate 93-94% of 1-chloroanthraquinone with m.p. 157-159°.

Preparation of complexes of copper salts with aniline. To a solution of 28 g of aniline in 80 ml of benzene was added at 20-25°, with good stirring, 0.1 mole of anhydrous copper acetate or some other copper salt. The color of the reaction mass changed from yellow to dark green. The suspension was heated to 70° and stirred at this temperature for 1 hr, after which the formed complex was allowed to stand for several hours to crystallize. The obtained

precipitate was filtered, repeatedly washed with benzene to remove excess aniline, and air-dried. The yield of the complex $2Cu(CH_3COO)_2 \cdot 3C_6H_5NH_2$ was 28.3 g (85%). The compounds $CuCl_2 \cdot 2C_6H_5NH_2$; $CuBr_2 \cdot C_6H_5NH_2$; $CuSO_4 \cdot$ $\cdot C_6H_5NH_2$ were obtained under the same conditions.

Acid hydrolysis of complexes of copper salts with aniline. A weighed amount of the complex (2-3 g) was heated under reflux for 2-3 hr with 100 ml of 10-15% aqueous hydrochloric or sulfuric acid solution. Here the precipitate gradually went into solution. Then the mixture was filtered from a small amount of dark turbidity, the filtrate was made up to volume with water in a 500 ml volumetric flask, and the amounts of copper and appropriate anion were determined using conventional techniques. The aniline was determined by diazotization after separation from Cu^{++} ion. For this 100 ml of the solution was pipetted into a separatory funnel, neutralized with either ammonia or ammonia-containing caustic, and the aniline was extracted with benzene from the weakly alkaline blue solution. After separating the water layer, the benzene layer was shaken with 5% hydrochloric acid solution in the same separatory funnel. Then the aqueous hydrochloric acid layer was separated and the aniline was diazotized in conventional manner with 0.1 N sodium nitrite solution.

Reaction of aniline hydrohalide with $2Cu(CH_3COO)_2 \cdot 3C_6H_5NH_2$ (I). To a suspension of 15.1 g of (I) in 100 ml of aniline was added at 20°, with good stirring, 0.05 mole of either aniline hydrochloride or hydrobromide. Then the mixture was heated to 90-95° and held at this temperature with stirring for 1 hour, after which it was cooled to +5° and the precipitate of complex (II) or (III) was filtered, washed slightly with aniline, and then with benzene to remove the aniline. The weight of complex (II) was 6.3 g, and that of complex (III) was 7.1 g. The composition of the complexes is given in Table 3.

The aniline filtrate had a strong odor of acetic acid. The mixture of aniline and acetic acid was vacuum-distilled (12 mm, 70-75°) to yield 70 ml of distillate. The acetic acid was extracted from the mixed distillate by shaking with water, followed by separation of the water layer and titration with 0.5 N sodium hydroxide solution. In this way we obtained 4.05 g of acetic acid.

SUMMARY

1. The catalytic activity of 11 copper compounds in the reaction of 1-chloroanthraquinone with excess aniline in the presence of potassium acetate was examined.

2. It was shown that the catalytic activity of the copper compound is influenced more by the nature of the anion than by the valence of the copper.

3. It was found that when the reaction is run in the absence of acid-binding agents the cleaved hydrogen halide adds to the copper acetate-aniline complex, displacing the acetic acid radical and greatly reducing the activity of the catalyst.

4. Side reactions caused by the presence of copper compounds were observed in the aramination. These side reactions were the formation of small amounts of azobenzene and partial halogenation of the anilinoanthraquinone.

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SYNTHESIS OF SOME DERIVATIVES OF 4,5,6,7-DIBENZO-1,3-DIAZA-2,4,6-CYCLOHEPTATRIENE

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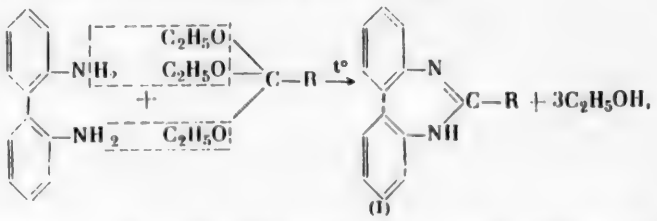
4,5,6,7-Dibenzo-1,3-diaza-2,4,6-cycloheptariene (I) was first obtained by Sako [1].

Compounds (Ib) and (Ie) were synthesized by heating the corresponding monoacyl derivatives of o,o'-diaminobiphenyl with phosphorus trichloride, while the hydrochloride of (Ia) was obtained by treating the N,N'-diformyl derivative of this amine with dry hydrogen chloride in boiling xylene. By using the levo- and dextro-rotatory o,o'-diamino-o-ditolyls it also proved possible to obtain the optically active isomeric seven-membered heterocycles, which testifies to their complex nonplanar spatial configuration. In addition, compound (Id) was obtained [2] by heating nonyl cyanide with o,o'-diaminobiphenyl benzenesulfonate.

We developed a one-step method for obtaining derivatives of system (I), starting with o,o'-diaminobiphenyl and orthoesters. The reaction proceeds in accordance with the scheme:

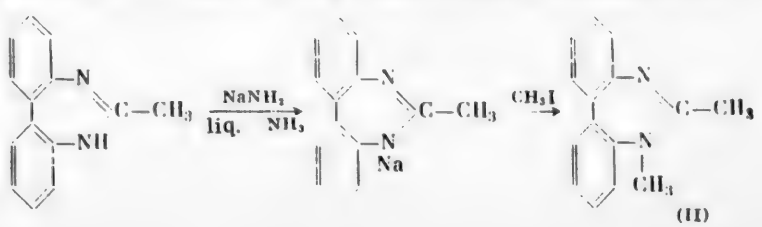


(I)

a) R = H, b) R = CH_3, c) R = C_2H_5, d) R = n-C_9H_{19}, e) R = C_6H_5

i.e., it is an expansion into the series of seven-membered heterocycles of the known method of synthesizing N,N'-diarylamidines (linear products) and benzimidazoles (five-membered heterocycles) from orthoesters and the appropriate amines. With this method we obtained compounds (Ib) and (Ic) and also (Ia) as the hydrochloride, since the free base, in accordance with the literature data [1], does not crystallize. The compound obtained most rapidly and in the best yield is (Ib). The long heating of o,o'-diaminobiphenyl with orthoformic ester yields a high melting, difficultly soluble product, which in its composition approaches that of (Ia). However, a more detailed study of this product was not made. It could possibly be the polyamidine.

Sako attempted to replace the hydrogen atom in the NH group of compound (Ib) by the methyl group, treating this compound under various conditions with methyl iodide. However, he constantly obtained only the products of the reductive cleavage of the heterocycle. Our attempts to use dimethyl sulfate as the methylating agent also failed to yield the desired product. However, it proved that the tertiary base could be easily obtained in very good yield by methylating the sodium salt of compound (Ib) in liquid ammonia with methyl iodide.



(II)

It is interesting that solutions of the sodium salt of (Ib) and of tertiary base (II) in liquid ammonia are intensely colored in different shades of red. Product (II) can be converted to the quaternary salt (III) by treatment with dimethyl sulfate in boiling benzene. With p-dimethylaminobenzaldehyde in the presence of zinc chloride, salt (III) gives an orange dye with λ_{max} 480 mμ.

EXPERIMENTAL

Preparation of hydrochloride of (Ia). A mixture of 2.6 g of o,o'-diaminobiphenyl and 2.1 g of orthoformic ester was heated under reflux in an oil bath at 140-150° for 3 hr. After cooling, the noncrystallizing viscous mass was treated with 5 N hydrochloric acid until acid to Congo, diluted with water until a precipitate appeared, and then allowed to stand overnight in the cold. The pale yellow crystalline precipitate was filtered and dried over sulfuric acid. Yield 1.0 g (31%). M.p. 244-247°; from the literature, m.p. 245-246° [1].

A dense yellow precipitate was gradually formed if the heating was maintained for more than 3 hr. This precipitate was insoluble in alcohol, ether, benzene, dioxane and other organic solvents, and soluble in hydrochloric and hot acetic acids. M.p. 264-267°.

Found %: C 78.7, 78.7; H 5.0, 5.1. $(C_{13}H_{10}N_2)_x$. Calculated %: C 80.4; H 5.2.

Hydrochloride, m.p. 229-232°.

Found %: Cl 14.7, 14.8. $(C_{13}H_{10}N_2 \cdot HCl)_x$. Calculated %: Cl 15.4.

Compound (Ib). A mixture of 3.5 g of o,o'-diaminobiphenyl and 3.1 g of ethyl orthoacetate in a small flask fitted with a reflux condenser was placed in an oil bath, heated to 140°. A vigorous frothing of the reaction mixture took place, and after 1-2 min a yellow precipitate deposited. Heating at 140-150° was continued for several minutes more and then the mixture was cooled. The precipitate was separated, washed with a little alcohol, and dried. We obtained 2.74 g (70%) of compound (Ib) as a yellow crystalline powder. M.p. 223.5-225.5° (from aqueous alcohol). From the literature: m.p. 228° [1].

Found %: C 80.5, 80.8; H 5.9, 6.0. M 203, 208. $C_{14}H_{12}N_2$. Calculated %: C 80.6; H 5.8. M 208.

The hydrochloride was a yellow crystalline powder. M.p. 199.5-201.5° (from water); from the literature: m.p. 202-203° [1].

Compound (Ic). A mixture of 1.0 g of o,o'-diaminobiphenyl and 1.0 g of ethyl orthopropionate was heated under reflux in an oil bath at 110-120° for 3 hr; here a yellow crystalline precipitate gradually formed. The reaction was completed by heating to 170°. After cooling, the semicrystalline mass was dissolved in the minimum amount of alcohol, and the solution on cooling to 0° deposited compound (Ic) as a yellow crystalline powder. M.p. 160-161°. Yield 0.41 g (34%). M.p. 161-162° (from alcohol).

Found %: N 12.7, 12.8. $C_{15}H_{14}N_2$. Calculated %: N 12.6.

Compound (II). Three grams of compound (Ib) were added to a suspension of sodium amide, obtained from 0.33 g of sodium in 50 ml of liquid ammonia; here the precipitate went into solution, which assumed a dark red color. After 1 hr 2.06 g of methyl iodide was added to the solution. A precipitate deposited immediately, but the solution remained red. The liquid ammonia was evaporated, and the nearly colorless residue was washed well with water. Yield 2.8 g (87%); colorless crystalline powder, insoluble in water, and soluble in most organic solvents. M.p. 89-92°. After recrystallization from carbon tetrachloride, m.p. 89.5-92.5° (cloudy melt).

Found %: C 81.1, 81.1; H 6.1, 6.2. $C_{15}H_{14}N_2$. Calculated %: C 81.0; H 6.3.

Compound (III). A mixture of 0.60 g of compound (II), 0.34 g of dimethyl sulfate and 10 ml of benzene was heated under reflux for 12 hr. Here a brown oil gradually collected on the bottom of the flask, and toward the end of heating it partially crystallized. After cooling, the benzene was decanted and the semisolid product was triturated with anhydrous alcohol. The nearly colorless crystalline substance was filtered, washed, and dried over sulfuric acid. The yield of the methyl sulfate of (III) was 0.11 g (11.7%).

Found %: S 9.3, 9.1. $C_{17}H_{20}O_4N_2S$. Calculated %: S 9.2.

SUMMARY

1. Some derivatives of 4,5,6,7-dibenzo-1,3-diaza-2,4,6-cycloheptatriene were synthesized by reacting o,o'-diaminobiphenyl with orthoesters.

2. The tertiary base and the quaternary salt, derivatives of this heterocyclic system, were obtained for the first time.

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MONOORGANOSILANES

I. SYNTHESIS OF MONOORGANOSILANES

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Organosilicon compounds, containing hydrogen atoms on the silicon, steadily attract the attention of investigators. This is due to the high reactivity and peculiar nature of the Si–H bond, which opens up broad possibilities for both theoretically and practically important syntheses. Up to now chief consideration has been given to the triorganosilanes R_3SiH and in part to the diorganosilanes R_2SiH_2. The monoorganosilanes $RSiH_3$ have received little study, although these compounds represent undoubted theoretical interest and possess much promise for practical use.

In view of the analogy between the $-CH_3$ and $-SiH_3$ groups, but because of their opposite polarization, new possibilities open up for studying the questions pertaining to the mutual influence exerted by atoms in the molecules of organic compounds.

When monoorganosilanes are reacted with the appropriate reagents in accordance with the scheme:

$$RSiH_3 \xrightarrow[-H_2]{+R'H} RSiH_2R' \xrightarrow[-H_2]{+R'H} RSiHR_2' \xrightarrow[-H_2]{+R'H} RSiR_3'$$

it becomes possible to establish the relative reactivity of the Si–H bonds in mono-, di-, and tri-organosilanes and its dependence on the nature of both the original radical and the radicals entering into the molecule.

The high reactivity of the monoorganosilanes opens up broad possibilities for the synthesis of organosilicon compounds, capable of further transformations into technically valuable products.

At the time that we started our work, the synthesis of monoorganosilanes was described by only a few investigators. Thus, Stock and Somieski [1] obtained methylsilane by reacting chlorosilane with dimethylzinc; Finholt and coworkers [2] synthesized a number of alkylsilanes by the reduction of the corresponding alkyltrichlorosilanes with aluminum lithium hydride, while Nebergall [3] obtained phenylsilane in a similar manner; Hurd [4] patented the synthesis of organosilanes from silane and olefins under pressure.

In 1951, we proposed a method for the synthesis of monoalkylsilanes that was analogous to the procedure described by Whitmore and coworkers [5] for the synthesis of diorganosilanes. This method consisted in reacting alkyltrichlorosilanes with trialkylsilanes in the presence of aluminum chloride in accordance with the scheme:

$$3R_3SiH + R'SiCl_3 \xrightarrow{AlCl_3} 3R_3SiCl + R'SiH_3$$

Stoichiometric amounts of the reactants were heated in the presence of 2-4 mole % of anhydrous $AlCl_3$, in which the formed alkylsilane was removed continuously by distillation through a column packed with spiral packing; the reaction was considered ended when the temperature in the reaction flask reached the boiling point of the corresponding trialkylchlorosilane.*

* The proposed method was confirmed by B. N. Dolgov, S. N. Borisov, and M. G. Voronkov [6], who did the work in 1957 on the basis of our data.

With this method we synthesized the n-butyl- and isoamylsilanes, in which connection as hydrogen donors we used various trialkylsilanes: triethyl-, tri-n-butyl-, and triisoamylsilane.

It proved that the yield of butylsilane from butyltrichlorosilane changed as a function of the nature of the trialkylsilane in the following manner: $(C_2H_5)_3SiH$ – 83%, $(C_4H_9)_3SiH$ – 73%, $(iso\text{-}C_5H_{11})_3SiH$ – 47%. The yield of isoamylsilane from isoamyltrichlorosilane and tributylsilane was 60%.

As a result, the proposed and studied reaction possesses a general character and leads to obtaining the corresponding alkylsilanes, independent of the nature of the radicals, attached to the silicon atoms of the two reactants. However, the reactivity of the alkyltrichloro- and trialkylsilanes decreases with increase in the chain length and molecular weight of the alkyl radicals.

It was known [2] that the tri- and dialkylsilanes can be obtained by the reduction of the corresponding alkylchlorosilanes with lithium hydride. This method was extended by us to the synthesis of monoorganosilanes in accordance with the scheme

$$RSiCl_3 + 3LiH \longrightarrow RSiH_3 + 3LiCl$$

The reaction goes smoothly and in satisfactory yields if the organotrichlorosilane is added gradually to a suspension of excess lithium hydride in anhydrous boiling dioxane with vigorous stirring, followed by heating the reaction mixture under reflux for 1-2 hr and then distilling off the liquid products. All of the operations must be conducted in a nitrogen atmosphere. With this procedure we synthesized the butyl-, phenyl-, isoamyl-, and p-chlorophenylsilanes. The first two products are well known, isoamylsilane is new, while p-chlorophenylsilane is mentioned only in the patent literature [7].

The need to conduct the syntheses in an atmosphere of dry, oxygen-free nitrogen is linked with the possibility of forming silane, SiH_4, as the result of disproportionation of the obtained monoorganosilane when heated and, possibly, under the influence of the components of the reaction mixture:

$$2RSiH_3 \longrightarrow R_2SiH_2 + SiH_4$$

The formation of silane is extremely undesirable, and with the slightest neglect it can be the reason for explosion or ignition. It was observed that the ease with which silane is formed depends on the character of the organic radical attached to the silicon. Thus, only trace amounts of SiH_4 are formed in the synthesis of butylsilane and isoamylsilane, and the process can even be run in the absence of nitrogen, the vapors of the solvent serving as protection. The use of nitrogen is completely obligatory in the preparation of phenylsilane, since the admittance of air to the reaction flask causes explosion. In the case of p-chlorophenylsilane the evolution of silane is so great that the gas escaping from the system catches fire. Consequently, in the synthesis of p-chlorophenylsilane it is necessary to use the following technique: immediately after adding the p-chlorophenyltrichlorosilane to a suspension of a slight excess (20%) of lithium hydride in boiling dioxane, the reaction flask is cooled and the precipitate is filtered in a stream of nitrogen. The fractional distillation of the filtrate proceeds without difficulty.

It should be pointed out that the ability to form silane, descending in the order p-chlorophenylsilane > phenylsilane > butylsilane, can serve as a criterion of the reactivity of monoorganosilanes as a function of the nature of the organic radical attached to the silicon.

EXPERIMENTAL

Starting products. Butyltrichlorosilane, isoamyltrichlorosilane, phenyltrichlorosilane, trichlorosilane, tributylsilane, triethylsilane and triisoamylsilane were synthesized by conventional procedures. The technical lithium hydride, after grinding in a ball mill and shifting, contained 80-85% LiH.

p-Chlorophenyltrichlorosilane [8]. A mixture of 90.6 g of phenyltrichlorosilane and 1.45 g of $SbCl_3$ was placed in a flask fitted with a stirrer, thermometer, sparger for the addition of chlorine and a reflux condenser, connected to wash bottles filled with NaOH solution.

The chlorination was run at 40-50° until the increase in the weight of the wash bottles was 14-15 g. The chlorination products were fractionally distilled through a vacuum rectification column. We obtained 13.7 g of a fraction with b.p. 75-78° at 9 mm – phenyltrichlorosilane, 5.0 g of a fraction with b.p. 78-96° at 9 mm – a mixture of

phenyltrichlorosilane and m- and p-chlorophenyltrichlorosilanes, and 61.0 g of a fraction with b.p. 96-98° at 9 mm – p-chlorophenyltrichlorosilane. The phenyltrichlorosilane was analyzed; n_D^{20} 1.5400.

Found %: Si 10.95; hydrolyzable Cl 43.2; total Cl 56.3. $C_6H_7SiCl_4$. Calculated %: Si 11.75; hydrolyzable Cl 43.5; total Cl 57.7.

Reaction of Alkyltrichlorosilanes with Trialkylsilanes

Butyltrichlorosilane and triethylsilane. With vigorous stirring, 0.016 g mole of $AlCl_3$ was added to a mixture of 0.2 g mole of butyltrichlorosilane and 0.6 g mole of triethylsilane. The reaction flask was then attached to a rectification column (10 theoretical plates) and the mixture was boiled with continuous removal of the fraction with b.p. 55-56°, representing pure butylsilane.

The reaction was considered ended when the temperature in the reaction flask reached 145°. The yield of butylsilane was 14.28 g (83.1%).

B. p. 55-56°, n_D^{20} 1.3942, d_4^{20} 0.6794, MR_D 31.05; calc. 31.00.

Found %: H_{act} 3.26. $C_4H_{12}Si$. Calculated %: H_{act} 3.43.

Butyltrichlorosilane and tributylsilane. In a similar manner from 0.14 g mole of butyltrichlorosilane, 0.43 g mole of tributylsilane and 0.012 g mole of $AlCl_3$, and a final temperature in the flask of 250°, we obtained 8.93 g (73.6%) of butylsilane, b.p. 55-56°.

Butyltrichlorosilane and triisoamylsilane. In a similar manner from 0.11 g mole of butyltrichlorosilane and 0.33 g mole of triisoamylsilane in the presence of 0.018 g mole of $AlCl_3$, and a final temperature in the flask of 250°, we obtained 4.45 g (46.5%) of butylsilane, b.p. 55-56°.

Isoamyltrichlorosilane and tributylsilane. In a similar manner from 0.108 g mole of isoamyltrichlorosilane and 0.325 g mole of tributylsilane in the presence of 0.015 g mole of $AlCl_3$ we obtained 6.5 g (59.3%) of isoamylsilane.

B. p. 75.4-76.0°, d_4^{20} 0.6841, n_D^{20} 1.4010, MR_D 36.20; calc. 35.75.

Found %: H_{act} 2.98. $C_5H_{14}Si$. Calculated %: H_{act} 2.94.

Synthesis of Silanes by Reacting Organotrichlorosilanes with Lithium Hydride

Butylsilane. Into a flask fitted with a ground-glass stirrer, reflux condenser, dropping funnel, thermometer and gas-inlet tube, after blowing with nitrogen, was charged 200 ml of anhydrous dioxane and 10 g of finely pulverized lithium hydride. The suspension was heated to reflux and then with vigorous stirring, in a stream of nitrogen, 38 g of butyltrichlorosilane was added in 1 hour. After heating under reflux for 1 hour, the reaction flask was cooled and connected to a descending condenser (in a stream of nitrogen!), after which all of the liquid products were distilled, followed by their fractionation through a column (30 theoretical plates). We obtained 11.5 g (66%) of butylsilane with b.p. 55-56°.

Isoamylsilane. In a similar manner from 20 g of isoamyltrichlorosilane and 5 g of lithium hydride (LiH content 60%) in 50 ml of anhydrous dioxane we obtained 4.28 g (43.1%) of isoamylsilane with b.p. 75-76°.

Phenylsilane. In a similar manner from 116 g of phenyltrichlorosilane and 26 g of lithium hydride in 250 ml of anhydrous dioxane we obtained 45.1 g (76.3%) of phenylsilane with b.p. 119-120° and n_D^{20} 1.5089.

Found %: H_{act} 2.76. C_6H_8Si. Calculated %: H_{act} 2.77.

p-Chlorophenylsilane. The synthesis was run in the above described apparatus. To a boiling suspension of 10 g of lithium hydride in 150 ml of anhydrous dioxane was added 52 g of p-chlorophenyltrichlorosilane in 1 hour, after which the reaction flask was cooled, the precipitate was filtered on a glass filter in a stream of nitrogen, washed with dioxane, and the filtrate was fractionally distilled through a column. The first to distill was the dioxane, b.p. 102-158° (2 g), and then the p-chlorophenylsilane – 16.3 g (56.5%).

B.p. 162-163°, d_4^{20} 1.0683, n_D^{20} 1.5340, MR_D 41.35; calc. 41.62.

Found %: H_{act} 2.13. C_6H_7SiCl. Calculated %: H_{act} 2.10.

SUMMARY

1. We developed and studied a general method for the synthesis of alkylsilanes, which was based on reacting alkyltrichlorosilanes with trialkylsilanes in the presence of $AlCl_3$. It was shown that the yield of the reaction product depends on the nature of the radicals attached to the silicon.

2. A number of monoorganosilanes were synthesized by the reduction of the corresponding monoorganotrichlorosilanes with lithium hydride. The theory was expressed that the formation of silane, accompanying this reaction, is due to disproportionation of the monoorganosilanes, the ability of which to disproportionate decreases in the order p-chlorophenylsilane > phenylsilane > butylsilane.

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REACTION OF ACETOACETIC ESTER WITH BENZENE IN THE PRESENCE OF $AlCl_3$

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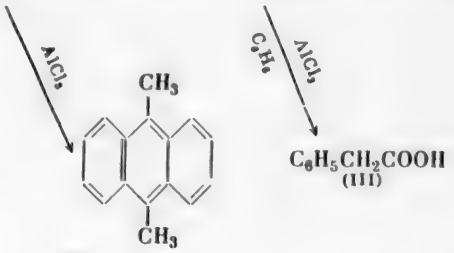
The results obtained in studying the reaction between acetoacetic ester and benzene in the presence of $AlCl_3$ are reported in this paper.

Information on the condensation of acetoacetic ester with aromatic hydrocarbons is lacking in the literature, although in general the alkylation of acetoacetic ester has been studied in detail [1].

It was established by many authors that the reaction of aromatic hydrocarbons with the ester of mono- and dibasic acids in the presence of anhydrous $AlCl_3$ can go in two directions: either with the formation of alkyl derivatives of benzene [2-4, 7], or with the formation of aryl ketones [3, 5, 6].

In the presence of 2 g moles of $AlCl_3$, acetoacetic ester alkylates benzene, and ethylbenzene (I) is formed in up to 27.2% yield.

$$CH_3COCH_2COOC_2H_5 + C_6H_6 \xrightarrow{AlCl_3} \underset{(I)}{C_6H_5CH_2CH_3} + CH_3COCH_2COOH \rightarrow CH_3COCH_3 + CO$$



(IV)

Increasing the reaction time and heating on the water bath leads to the formation of 9,10-dimethylanthracene (IV) as the result of further condensation of the ethylbenzene.

Ethylbenzene was identified by its physical constants (density, refractive index), its molecular weight, and as the result of its oxidation to benzoic acid.

The reaction of benzene with acetoacetic ester yields a small amount of phenylacetic acid.

The formation of products deriving from reaction of the ketone group could not be detected. This is in accord with the data on the condensation of diacetone alcohol with benzene [8].

The cleavage products of the acetoacetic ester were not investigated.

EXPERIMENTAL

The experiment giving the best results will be described.

The reaction was run in a three-necked flask fitted with a reflux condenser and a thermometer. To a mixture, composed of 10.7 g of acetoacetic ester and 60 ml of benzene, was gradually added, in portions, 23.0 g of $AlCl_3$ in 0.5 hr. Then, with the stirring, the heating was continued on the water bath (70-80° in the flask) for another 3 hr.

With cooling, the reaction mixture was decomposed with acidulated water, after which the top layer was separated and dried over Na_2SO_4.

After distilling off the benzene we obtained a fraction with b.p. 105-155° (5.2 g). Redistillation of this fraction from sodium gave 2.3 g of ethylbenzene (I) fraction.

B. p. 132-136°, d_4^{20} 0.8676, n_D^{20} 1.4942, M 10.5. Literature data for ethylbenzene: b. p. 136°, d_4^{20} 0.86690, n_D^{20} 1.49594 [9].

The residue with b.p. above 155° (1.45 g) soon crystallized to yellow crystals with m.p. 174-179° (from benzene) (II).

Fractional crystallization of substance (II) from benzene led to the isolation of a substance with m.p. 76° (III) and a substance with m.p. 182-183° (IV).

The mixed melting point of (III) with authentic phenylacetic acid was not depressed [9].

Substance (IV) proved to be 9,10-dimethylanthracene.

A mixture of 10.6 g of ethylbenzene, 50 ml of benzene and 20.0 g of $AlCl_3$ was heated on the boiling water bath for 3.5 hr. After the usual treatment we isolated 2.9 g of 9,10-dimethylanthracene with m.p. 182° (from benzene) [10].

The mixed melting point of (IV) with 9,10-dimethylanthracene was not depressed.

Oxidation of compound (I). For the oxidation we took 1.5 g of (I), 10.0 g of $KMnO_4$ and 200 ml of water. The solution decolorized after heating for 6 hr. Then the solution was filtered and the filtrate was evaporated to a small volume; the oxidation product was isolated by the addition of concentrated hydrochloric acid. The isolated substance, after recrystallization from water, had m.p. 120-121°.

The mixed melting point with pure benzoic acid was not depressed.

SUMMARY

The reaction of acetoacetic ester with benzene in the presence of 2 g moles of $AlCl_3$ results in alkylation of the benzene with the formation of ethylbenzene in up to 27.2% yield.

9,10-Dimethylanthracene and phenylacetic acid are formed along with the ethylbenzene.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

IMIDAZOLE DERIVATIVES

XXV. 4,5-DIMETHOXYL DERIVATIVES OF 2-BENZIMIDAZOLINONE

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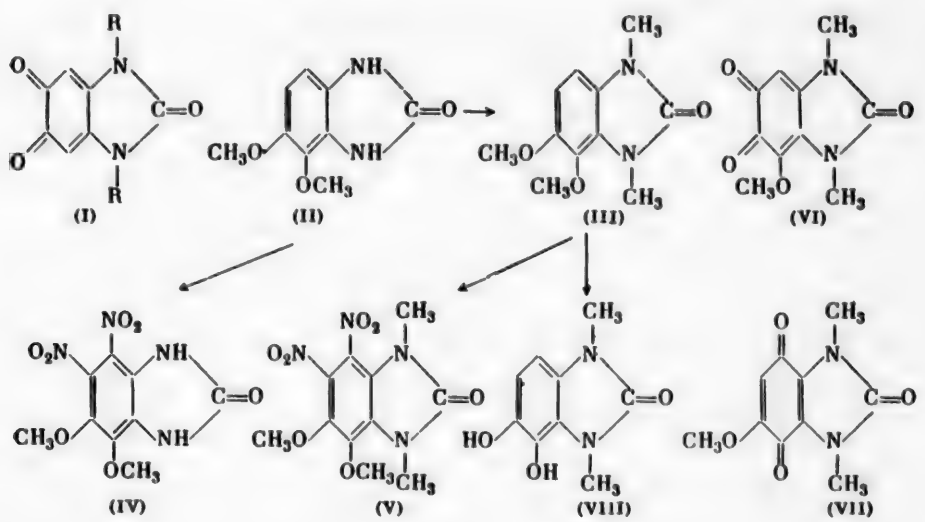
Previously we had established [1] that the 5,6-dioxo compounds (I) of 2-benzimidazolinone, easily formed in the oxidation of not only the 5,6-dihydroxy, but also the 5,6-dimethoxy and 5-methoxy-6-chloro derivatives, are characterized by a high stability and a comparatively low redox potential value, close to the redox potential value of 1,2-naphthoquinone. We explained the chemical behavior shown by these compounds as due to the influence exerted by the imidazolinone ring on the benzene ring condensed with it, leading to a marked increase in the degree of unsaturation between the 5 and 6 carbon atoms of the molecule. It was shown by us that the reactivity of substituents attached to this linkage in 2-benzimidazolinone is completely analogous to that exhibited by substituents attached to the 1-2 linkage in naphthalene [2].

Developing a comparison in the properties of naphthalene and 2-benzimidazolinone, it could be assumed that a similarity exists in the state and reactivity of the linkages between the 4-5 and 2-3 positions in 2-benzimidazolinone and naphthalene, respectively. The closeness of the 2-3 linkage in naphthalene to a single bond determines, in part, the instability of the 2-3 quinone, not obtained up to now and apparently possessing a very high redox potential.

In the case of 2-benzimidazolinone it could be expected that the 4-5 linkage will be of a lower order than the C–C bond in benzene and consequently the 4,5-dioxo compounds will be difficultly available and, in any case, quite unstable.

To verify this assumption, we undertook the synthesis of the previously unknown 4,5-dimethoxy-2-benzimidazolinone (II) and its 1,3-dimethyl derivative (III). We obtained the first compound in conventional manner by fusing urea with 3,4-diaminoveratrole. The latter was synthesized by a multistep process, starting with the acetyl derivative of vanillin [3].

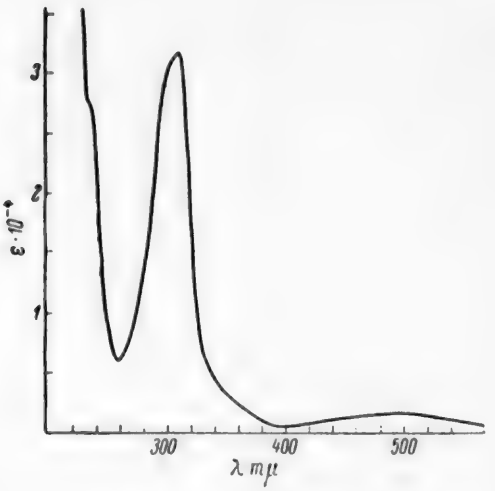


In contrast to the corresponding 5,6-dimethoxyl compounds, which are easily converted to quinones, it proved that dimethoxy derivatives (II) and (III) are not oxidized when treated with such oxidizing agents as ferric chloride, nitrous acid, or nitric acid.

In the last case nitration took place smoothly with the formation of dinitro derivatives (IV) and (V).

It proved that 4,5-dimethoxy-1,3-dimethyl-2-benzimidazolinone (III) could be oxidized only with cerium sulfate in acid medium. The compound that was isolated here had the composition $C_{10}H_{10}O_4N_2$, m.p. 206.5°, contained a methoxyl group, and was reduced by sodium hydrosulfite to yield a colorless compound. On the basis of these properties, the compound with m.p. 206.5° could be assigned the structure of either the o- or p-quinone, respectively either (VI) or (VII).

The electronic spectrum of the product with m.p. 206.5° was analogous to the spectra of 5,6-dioxo-2-benzimidazolinone and its 1,3-dimethyl analog (Figure, see [1]); however, in contrast to the latter, the position of the absorption maximum in the visible portion of the spectrum was practically independent of the nature of the solvent. In addition, the condensation product of the compound with m.p. 206.5° and o-phenylenediamine did not contain a methoxyl group [4].



Absorption spectrum of methanol solution of 4-methoxy-5,6-dioxo-1,3-dimethyl-2-benzimidazolinone*; λ_{max} 310 and 492 mμ, λ_{min} 258 and 405 mμ.

These properties caused us to assign the structure of the p-quinone (VII) to the compound with m.p. 206.5°. In latter papers we will report on the attempted counter synthesis of quinones (VI) and (VII).

The 4,5-dihydroxy compound (VIII), obtained by the dimethoxylation of product (III) using concentrated hydrobromic acid, proved to be extremely unstable in alkaline medium. Alkaline solutions of the compound are rapidly oxidized in the air to give red-colored products that could be purified only with great difficulty. Not one of these products gave gave a positive test for an o-quinone. The oxidation of a water suspension of dihydroxy compound (VIII) with ferric chloride gave a blue-colored compound of composition $C_{18}H_{16}O_5N_4$, which apparently was the dimerization product of the dihydroxy compound. Reacting readily with o-phenylenediamine in acetic acid solution, this compound forms an azine that is soluble in alkalies and is easily oxidized in the air.

As a result, also in the case of the dihydroxy compound (VIII) we were unable to isolate the 4,5-dioxo derivative of 2-benzimidazolinone.

The chemical properties of the 4,5-disubstituted derivatives of 2-benzimidazolinone studied in the present paper testify to the decreased order of the 4-5 linkage in 2-benzimidazolinone, in this way confirming the validity of our conclusions relative to the deformation of the π-electron cloud of this heterocycle and our analogies between 2-benzimidazolinone and naphthalene.

EXPERIMENTAL

4,5-Dimethoxy-2-benzimidazolinone (II). A mixture of 10 g of 3,4-diminoveratrole, obtained in 90% yield by the reduction of 3-nitro-4-aminoveratrole [3] over Raney nickel at 100 atm and 60-80°, and 10.5 g of urea was fused at 170-180° (bath temperature). On conclusion of reaction the solid melt was dissolved in 200 ml of 1 N NaOH. The solution after treatment with carbon was neutralized with hydrochloric acid, filtered, and the precipitate, after washing on the filter, was recrystallized from dioxane. Fine colorless crystals; yield 7.2 g, m.p. 246°. The compound is difficultly soluble in acetone, benzene or water, is readily soluble in acetic acid, and can be recrystallized from alcohol.

* An SF-4 spectrophotometer was used to take the spectrum at 2 mμ intervals, and at 1 mμ intervals in the region of the absorption extremes.

Found %: N 14.79, 14.78. $C_9H_{10}O_3N_2$. Calculated %: N 14.43.

4,5-Dimethoxy-1,3-dimethyl-2-benzimidazolinone (III). With vigorous stirring, 5 ml of dimethyl sulfate was added in drops to a solution of 5 g of 4,5-dimethoxy-2-benzimidazolinone in 50 ml of 2 N NaOH at 80°. After stirring at 90° for 30 min, the solution was treated with 6 g of NaOH and 5 ml of dimethyl sulfate. The reaction mass was refluxed for 30 min, evaporated to dryness, and extracted in an extractor with hot benzene. The residue from the evaporation of the extract was recrystallized from petroleum ether. Yield 60%. Slender colorless needles, m.p. 63.5°. The compound is readily soluble in water and in organic solvents.

Found %: N 12.96, 12.85. $C_{11}H_{14}O_3N_2$. Calculated %: N 12.61.

4,5-Dimethoxy-6,7-dinitro-2-benzimidazolinone (IV). One gram of 4,5-dimethoxy-2-benzimidazolinone was added in small portions, at 10-12°, with stirring, to 10 ml of HNO_3 (d 1.34). The reaction mass was cautiously heated to 40°, diluted with water, and the obtained precipitate was filtered, washed on the filter with water, and then recrystallized from 50% acetic acid. Yield 82%, m.p. 295° (decompn.). Fine yellow needles. The compound is difficultly soluble in organic solvents, and can be recrystallized from aqueous acetic acid, aqueous pyridine, or large volumes of alcohol.

Found %: N 19.67, 19.97. $C_9H_8O_7N_4$. Calculated %: N 19.72.

4,5-Dimethoxy-1,3-dimethyl-6,7-dinitro-2-benzimidazolinone (V) was obtained in the same manner as the above described nitro product. The yield of the crude product was 80%, m.p. 174° (from alcohol). Yellow needles.

Found %: N 17.82, 17.96. $C_{11}H_{12}O_7N_4$. Calculated %: N 17.95.

4,5-Dihydroxy-1,3-dimethyl-2-benzimidazolinone (VIII). A mixture of 1 g of 4,5-dimethoxy-1,3-dimethyl-2-benzimidazolinone and 7 ml of concentrated HBr was heated in a sealed tube for 2 hr at 150°. The precipitate was filtered and recrystallized from acetic acid. Fine colorless crystals, difficultly soluble in water and in organic solvents, m.p. 295° (with darkening).

Found %: C 55.95, 55.69; H 5.01, 4.95. $C_9H_{10}O_3N_2$. Calculated %: C 55.67; H 5.15.

5-Methoxy-4,7-dioxo-1,3-dimethyl-2-benzimidazolinone (VII). An excess of 0.1 N cerium sulfate solution in 1 N sulfuric acid was added at room temperature and with good stirring to a water solution of 4,5-dimethoxy-1,3-dimethyl-2-benzimidazolinone. The colored substance was extracted completely with chloroform, and the extract was dried over sodium sulfate, evaporated in vacuo, and the residue was repeatedly recrystallized from alcohol; m.p. 206.5°. The red needles of the quinone (VI) are soluble in organic solvents and insoluble in petroleum ether. Reduction of the compound with sodium hydrosulfite gave water-insoluble, colorless needles of the hydroquinone, which in alkaline medium were oxidized on exposure to the air. Decolorization is observed when water solutions of the quinone are treated with alkali, and then a blue-green color appears.

Found %: C 53.95, 53.96; H 4.69, 4.59; N 12.87, 12.74; OCH_3 14.53. $C_{10}H_{10}O_4N_2$. Calculated %: C 54.00; H 4.54; N 12.60; OCH_3 13.98.

Condensation of quinone (VII) with o-phenylenediamine. A solution of 0.17 g of quinone (VII) and 0.15 g of o-phenylenediamine in 4 ml of acetic acid was boiled for several minutes. The precipitate obtained on cooling was filtered and recrystallized from acetic acid, and then from alcohol. We obtained 0.11 g of pure compound as fine light-brown needles, beginning to decompose at 281°. The compound dissolves in concentrated H_2SO_4 with an orange-yellow color, and in alkali with a yellow-red color, and is precipitated on acidification [4]. For analysis the substance was dried at 110°.

Found %: N 19.68, 19.71. $C_{15}H_{12}O_2N_4$. Calculated %: N 20.00.

Oxidation of 4,5-dihydroxy-1,3-dimethyl-2-benzimidazolinone (VIII). An excess of aqueous ferric chloride solution was added to a fine suspension of 0.64 g of 4,5-dihydroxy-1,3-dimethyl-2-benzimidazolinone in 300 ml of water. After stirring for 30 min at room temperature the solution was extracted with chloroform (4 x 50 ml), and the extracts were washed twice with water, dried over magnesium sulfate, evaporated in vacuo to dryness, and the residue was recrystallized from a large volume of alcohol. We obtained 0.20 g of substance as fine dark-blue needles, difficultly soluble in water and in organic solvents; m.p. 262°. The compound is decolorized by sodium hydrosulfite solution, is instantly decomposed by sodium carbonate, and dissolves in concentrated H_2SO_4 with an intense reddish-purple color.

Found %: C 58.20; H 4.39; N 15.32. $C_{18}H_{16}O_5N_4$. Calculated %: C 58.70; H 4.38; N 15.20.

SUMMARY

The 4,5-dioxo compounds cannot be obtained by the oxidation of the 4,5-dimethoxy and 4,5-dihydroxy derivatives of 2-benzimidazolinone. This is explained by the reduced π-electron density of the 4-5 linkage in the benzimidazolinone.

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SYNTHETIC DYES

XXII. STYRYLS FROM DERIVATIVES OF N-ARYLQUINALDINIUM SALTS

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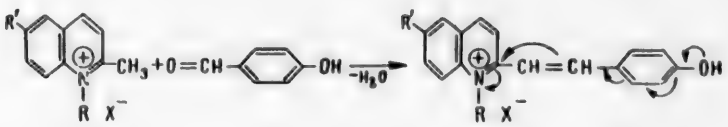
The literature contains a comparatively small number of investigations devoted to a study of hydroxystyryls. The first hydroxystyryl derivatives of N-methylquinaldinium salts were synthesized by the condensation of oxonium salts with hydroxybenzaldehydes [1]; Kiprianov and Petrun'kin [2] made a detailed study of the hydroxystyryls obtained from benzaldehydes and the alkyl halide salts of benzothiazole and quinaldine; Shulov [3] and Takahashi [5] made a study of the sensitizing properties of hydroxystyryls of diverse structure; Gilman and coworkers [4] synthesized and made a study of hydroxystyryls from the standpoint of their antiseptic and trypanocidal activity; Mushkalo [6] obtained and investigated the optical properties of the styryls derived from heptahydro-1,5-thiazine hydrochloride; a number of authors [7] have studied the anticarcinogenic activity of styryls of diverse structure.

Expanding our studies on the synthesis of styryl dyes by the condensation of the onium salts of arylquinaldinium derivatives with aromatic aldehydes and other carbonyl-containing organic compounds [8], we investigated a number of p-hydroxystyryls, attempting to establish the influence exerted by the OH group on the properties of the obtained dyes.

In this paper we discuss the synthesis and study of the styryls that we obtained by the condensation of N-arylquinaldinium salts with p-hydroxybenzaldehyde. The formation of the styryls went in accordance with the following scheme:



The spectral characteristics of the obtained styryls are given in the table.

From the spectroscopic data given in the table it can be seen that the p-hydroxystyryls obtained by us show a hypsochromic shift of about 90-100 mμ when compared with the p-aminostyryl and p-dimethylaminostyryl series of dyes, and a bathochromic shift of 18-20 mμ when compared with the analogous p-acetamidostyryls. Such a shift in the absorption maximum is in accord with the electronic structure of the compared dyes. In the case of the p-aminostyryls the observed hypsochromic shift of the absorption maximum when compared with the p-dimethylamino derivatives is explained by the more weakly expressed electron-donor properties of the amino group when compared with the dimethylamino group. Acetylation of the amino group gave a hypsochromic shift with respect to both the amino- and dimethylaminostyryls, which was caused by the electron-acceptor effect of the carbonyl group. Finally, for the discussed p-hydroxystyryls a hypsochromic shift of their absorption maxima when compared with the amino- and dimethylaminostyryls can be explained by the less effective participation of the free electron pairs of the oxygen atom in conjugation with the π-electrons of the main conjugation chain of the dye molecule.

EXPERIMENTAL

2-(p-Hydroxystyryl)-1-phenylquinolium perchlorate. A mixture of 0.45 g of 1-phenylquinaldinium perchlorate, 0.17 g of p-hydroxybenzaldehyde and 2 ml of pyridine was gently refluxed for 40 min. Then the reaction mass was transferred to a beaker and the dye was precipitated with ether. Recrystallization from alcohol gave the dye as yellow crystals with m.p. 260° (decompn.). Yield 0.24 g (40%).

Name of heterocycle	R	X	Absorption maxima of the styryls (in mμ)			
			hydroxy derivative*	acetamido derivative**	amino derivative**	dimethylamino derivative**
Quinaldine	C_6H_5	ClO_4	450	438	536	546
6-Methylquinaldine	$p\text{-}C_6H_4CH_3$	ClO_4	444	436	530	543
5,6-Benzoquinaldine	C_6H_5	I	457	444	530	552
5,6-Benzoquinaldine	$p\text{-}C_6H_4CH_3$	I	458	440	530	543
5,6-Benzoquinaldine	$\beta\text{-}C_{10}H_7$	ClO_4	458	440	530	548
6-Methylquinaldine	$\alpha\text{-}C_{10}H_7$	ClO_4	455	442	540	556

* An SF-2M spectrophotometer was used to take the spectra of the ethanol solutions.

** The values of the absorption maxima were taken from the literature [8].

Found %: N 3.12, 3.21. $C_{23}H_{18}O_5NCl$. Calculated %: N 3.30.

2-(p-Hydroxystyryl)-1-(p-tolyl)-6-methylquinolinium perchlorate. A mixture of 0.43 g of 1-(p-tolyl)-6-methylquinaldinium perchlorate, 0.14 g of p-hydroxybenzaldehyde and 3 ml of pyridine was heated in a paraffin bath for 50 min. The obtained dye was precipitated with ether, washed with water, and recrystallized from alcohol. We obtained 0.31 g (59%) of the dye with m.p. 240° (decompn.).

Found %: N 2.99, 3.04. $C_{25}H_{22}O_5NCl$. Calculated %: N 3.09.

2-(p-Hydroxystyryl)-1-phenyl-5,6-benzoquinolinium iodide. A mixture of 1 g of 1-phenyl-5,6-benzoquinaldinium iodide, 0.3 g of p-hydroxybenzaldehyde, 10 ml of anhydrous ethanol and a drop of piperidine was heated under reflux in an oil bath for 60 min. On conclusion of reaction the reaction mass was allowed to stand for 24 hr. The obtained green crystals of the styryl were filtered and then recrystallized from alcohol. We obtained 0.78 g (60%) of the dye with m.p. 318° (decompn.).

Found %: N 2.62, 2.73. $C_{27}H_{20}ONI$. Calculated %: N 2.79.

2-(p-Hydroxystyryl)-1-(p-tolyl)-5,6-benzoquinolinium iodide. An equimolecular mixture of 0.36 g of 1-(p-tolyl)-5,6-benzoquinaldinium iodide and 0.1 g of p-hydroxybenzaldehyde in 8 ml of anhydrous alcohol, containing a drop of piperidine, was heated under reflux in a paraffin bath for 40 min. After standing for 12 hr, the obtained dye was filtered and recrystallized from alcohol. Yield 0.2 g (45%) m.p. 303° (decompn.).

Found %: N 2.60, 2.64. $C_{28}H_{22}O_5NI$. Calculated %: N 2.71.

2-(p-Hydroxystyryl)-1-(β-naphthyl)-5,6-benzoquinolinium perchlorate. A mixture of 0.5 g of 1-(β-naphthyl)-5,6-benzoquinaldinium perchlorate, 0.13 g of p-hydroxybenzaldehyde, 12 ml of anhydrous alcohol and several drops of piperidine was heated in an air bath for 50 min under gentle reflux. After 10 hr the dye, obtained as dark crystals, was filtered and then recrystallized from alcohol. Yield 0.31 g (50%), m.p. 195° (decompn.).

Found %: N 2.52, 2.61. $C_{31}H_{22}O_5NI$. Calculated %: N 2.67.

2-(p-Hydroxystyryl)-1-(α-naphthyl)-6-methylquinolinium perchlorate. A mixture of 0.43 g of 1-(α-naphthyl)-6-methylquinaldinium perchlorate, 0.14 g of p-hydroxybenzaldehyde, 10 ml of anhydrous alcohol and a trace of piperidine was heated under gentle reflux in an oil bath for 70 min. The next day the obtained yellow-green crystals of the dye were filtered, followed by recrystallization from alcohol. We obtained 0.22 g (42%) of the compound with m.p. 190° (decompn.).

Found %: N 2.73, 2.78. $C_{28}H_{22}O_5NCl$. Calculated %: N 2.87.

SUMMARY

1. The condensation of N-arylquinaldinium quaternary salts of diverse structure with p-hydroxybenzaldehyde gave 6 new dyes of the styryl type.

2. The light-absorption maxima of the obtained dyes are shifted toward shorter wavelengths when compared with the corresponding dimethylamino derivatives, and toward longer wavelengths when compared with the acetamido analogs.

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NITRATION OF 1-METHYLANTHRAQUINONE

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Up to now 1-methylanthraquinone has been a difficultly available compound, and consequently its properties have received little study. The method devloped by us [1] for the preparation of 1-methylanthraquinone, consisting in the diene condensation of 1,4-naphthoquinone with piperylene and subsequent oxidation of the adduct, makes 1-methylanthraquinone quite readily available and opens up possibilities for its use as an intermediate in the synthesis of vat dyes. In this connection it seemed important to study the electrophilic and nucleophilic substitution reactions of 1-methylanthraquinone, since these reactions are not described in the literature. Only Fischer and Ziegler [2] obtained a mononitro-1-methylanthraquinone by treatment with nitric acid, and they did not establish the structure of the compound.

It was shown by us that 4-nitro-1-methylanthraquinone is formed when 1-methylanthraquinone is treated with mixed acid. Reduction of this compound with sodium sulfide gave 4-amino-1-methylanthraquinone, identical with the earlier described compound [3]. The latter may find use as a dye for chemical fibers. 4-Acetamido-1-methylanthraquinone and 4-benzamido-1-methylanthraquinone were synthesized by the acylation of 4-amino-1-methylanthraquinone. The oxidation of 4-nitro-1-methylanthraquinone with nitric acid under pressure gave 4-nitro-1-anthraquinonecarboxylic acid, which on reduction with sodium sulfide was converted to 4-amino-1-anthraquinonecarboxylic acid.

All of the compounds synthesized by us can be used as intermediates in the synthesis of vat dyes.

EXPERIMENTAL*

4-Nitro-1-methylanthraquinone. A solution of 2.10 g of 1-methylanthraquinone in 17 ml of concentrated sulfuric acid was cooled to 0° and then a mixture of 0.6 ml of 98.1% nitric acid and 8.5 ml of concentrated sulfuric acid was added in drops. The reaction mass was then stirred for 1 hr at 0-5°, after which it was poured into ice water. The obtained precipitate was filtered, washed with water, dried, and recrystallized from 32-50 parts of acetic acid. The yield of pure product was 2.00 g (79.2%). Yellow-brown crystals (from acetic acid), m.p. 261.1-261.5°. The mononitro-1-methylanthraquinone described in [2] has m.p. 252°.

Found %: C 67.26, 67.49; H 3.36, 3.22; N 5.21, 5.24. $C_{15}H_9O_4N$. Calculated %: C 67.42; H 3.37; N 5.24.

4-Amino-1-methylanthraquinone. With stirring, a mixture of 4.85 g of 4-nitro-1-methylanthraquinone and 9.7 g of sodium sulfide in 97 ml of water was heated under reflux for 2 hr. After cooling, the precipitate was filtered, washed with water, and dried. Yield 4.31 g (quantitative). Red-brown plates from aqueous acetic acid, m.p. 178.6-180.0°. From [3], m.p. 180-182°. The mixed melting point with the 4-amino-1-methylanthraquinone obtained by the procedure described in [3] was not depressed.

Found %: C 76.00, 75.71; H 4.50, 4.35; N 5.92, 6.14. $C_{15}H_{11}O_2N$. Calculated %: C 75.96; H 4.64; N 5.90.

4-Acetamido-1-methylanthraquinone. A mixture of 0.82 g of 4-amino-1-methylanthraquinone and 3.3 ml of acetic anhydride was refluxed for 2 hr. The precipitate was filtered, washed with water, and dried. Yield 0.56 g (58.2%). Dilution of the mother liquor with water gave an addition 0.29 g (30.1%) of product. Yellow-brown crystals from acetic acid, m.p. 185.6-186.0°.

Found %: C 73.26, 73.18; H 4.42, 4.38; N 4.97, 5.20. $C_{17}H_{13}O_3N$. Calculated %: C 73.11; H 4.30; N 5.02.

* All of the melting points are corrected.

4-Benzamido-1-methylanthraquinone. A mixture of 0.80 g of 4-amino-1-methylanthraquinone, 7.5 ml of chlorobenzene and 1.06 ml of benzoyl chloride was refluxed for 2 hr. The precipitate was filtered, washed with a little cold alcohol, and dried. Yield 0.61 g (52.8%). Yellow-brown crystals from acetic acid, m.p. 213.5-214.3°.

Found %: C 77.60, 77.68; H 4.45, 4.51; N 4.17, 4.35. $C_{22}H_{15}O_3N$. Calculated %: C 77.41; H 4.40; N 4.11.

4-Nitro-1-anthraquinonecarboxylic acid. A mixture of 3.00 g of 4-nitro-1-methylanthraquinone and 36 ml of 47% nitric acid was heated in a sealed glass tube at 170-180° for 5 hr. The precipitate was filtered, washed with water, and dried. The yield of crude product was 2.8 g (80.7%); it was free of the starting 4-nitro-1-methylanthraquinone and did not require reprecipitation from alkaline solution. Bright yellow crystals from acetic acid, m.p. 310-311° (decompn.).

Found %: C 60.81, 60.80; H 2.72, 3.10; N 4.47, 4.48. $C_{15}H_7O_6N$. Calculated %: C 60.60; H 2.36; N 4.68.

4-Amino-1-anthraquinonecarboxylic acid. A mixture of 1.09 g of 4-nitro-1-anthraquinonecarboxylic acid, 1.63 g of sodium sulfide and 35 g of water was refluxed for 2 hr. After cooling, the reaction mass was filtered and acidified with hydrochloric acid. The obtained precipitate was filtered, washed with water, and dried. Yield 0.98 g (quantitative). Red crystals from chlorobenzene, m.p. 241-241.5° (decompn.).

Found %: C 67.48, 67.54; H 3.52, 3.58; N 5.05, 4.97. $C_{15}H_9O_4N$. Calculated %: C 67.40; H 3.40; N 5.25.

SUMMARY

It was shown that the nitro group enters the 4 position when 1-methylanthraquinone is nitrated. We synthesized 4-amino-1-methylanthraquinone, its acetyl and benzoyl derivatives, and also the 4-nitro- and 4-amino-1-anthraquinonecarboxylic acids.

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CHANGES IN THE PROPERTIES OF SUBSTANCES IN DIFFERENT SERIES OF CHEMICAL COMPOUNDS

III. SERIES OF ISOPERIODIC COMPOUNDS

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In studying the properties of molecules, series of compounds are frequently discussed, the molecules of which differ, apart from the number of hydrogen atoms, only in the atoms of the elements of the same period (more accurately, series) in the periodic system [1]. It is of interest to also discuss the character of the changes in the values of the macrophysical properties of substances $-y_i-$ in the series of this type of isoperiodic compounds* [2]. Here it is obviously necessary to distinguish, independent of the presence or absence of a difference in the number of hydrogen atoms in the molecules, two types of the indicated series: with either the same (for example, the series:

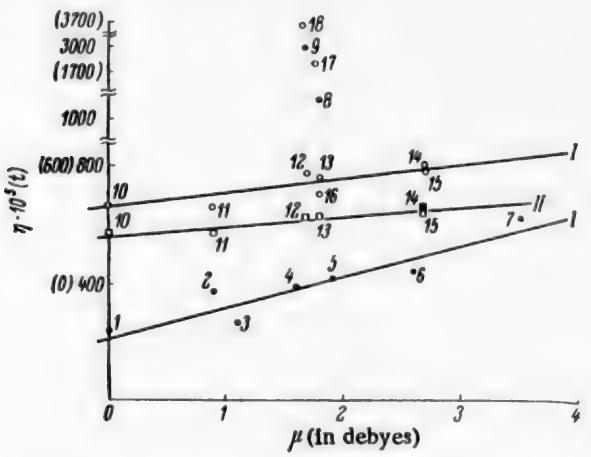

Fig. 1. Change in the value of $\eta \cdot 10^5$ in a series of isoperiodic compounds [I) 20°; II) 63°]. 1) n-C_5H_{12}; 2) $(C_2H_5)_2NH$; 3) n-$C_3H_7OCH_3$; 4) CH_3COOCH_3; 5) $HCOOC_2H_5$; 6) $CH_3COC_2H_5$; 7) n-C_3H_7CN; 8) C_2H_5COOH; 9) n-C_4H_9OH; 10) n-C_6H_{14}; 11) $C_2H_5OC_3H_7$-n; 12) $CH_3COOC_2H_5$; 13) $C_2H_5COOCH_3$; 14) $C_2H_5COC_2H_5$; 15) $CH_3COC_3H_7$-n; 16) n-$C_6H_{11}F$; 17) n-C_3H_7COOH; 18) n-$C_5H_{11}OH$.

n-$C_3H_7CH_3$, n-$C_3H_7NH_2$, n-C_3H_7OH, n-C_3H_7F, $C_2H_5OCH_3$, C_2H_5CHO, C_2H_5CN, CH_3COCH_3, $HCOOCH_3$) or different (for example, the series: $C(CH_3)_4$, $N(CH_3)_3$, $O(CH_3)_2$, FCH_3 or $Si(CH_3)_4$, $A_5(CH_3)_3$, $S(CH_3)_2$, ClCH) total number of atoms of the elements belonging to the same period (series) of the periodic system. In the series of the first type

* Also included here are the "pseudoatomic" series, "pseudo-rare gases," and homoform, isoelectronic and isosteric compounds [2, 3-5].

the molecules, possessing close values of the mass – m, size – V_M and polarizability – α, are distinguished essentially by the dipole moment – μ, and to a somewhat less degree by the details of the shape [6]; in the series of the second type the molecules are essentially distinguished by all of their indicated properties.

In the series of the first type a regular change is observed in the values of extremely different $(y_i)_{P,T}$ (P = = pressure, T = temperature) with change in the μ of the molecules. In accordance with the character of the influence exerted by cohesion forces on different y_i, the values of the latter for such properties as the friction coefficient – η, surface tension – γ, density – d, boiling point – T_b, etc. increase, while in the case, for example, of the

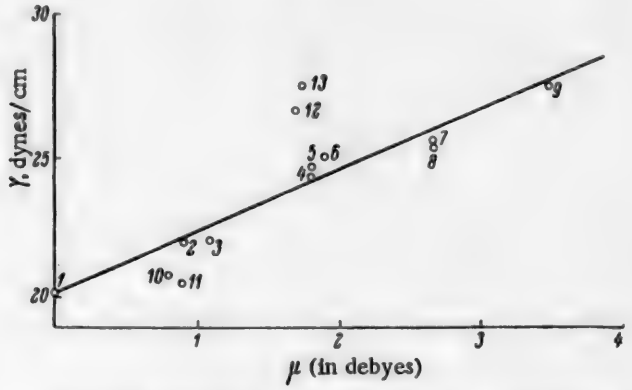

Fig. 2. Change in the values of γ (20°) in a series of isoperiodic compounds as a function of the dipole moment of the molecules. 1) n-C_6H_{16}; 2) (n-C_3H_7)$_2$NH; 3) n-$C_5H_{11}OCH_3$; 4) $CH_3COOC_3H_7$-n; 5) $C_2H_5COOC_2H_5$; 6) $CHCOOC_4H_9$-n; 7) n-$C_3H_7COC_2H_5$; 8) $CH_3COC_4H_9$-n; 9) n-$C_5H_{11}CN$; 10) $(C_2H_5)_3N$; 11) (n-C_3H_7)$_2$O; 12) n-$C_6H_{13}OH$; 13) n-C_4H_9COOH.

thermal coefficients of the density (K_d) and surface tension ($K\gamma$) they decrease with increase in the μ of the molecules of the members in the series. If it is assumed that when $\mu = 0$ the value $(y_i)_{P,T} = (y_i)_{P,T\,\mu\,=\,0}$, i.e., it is such for the nonpolar members of a given series, then it proves that for most members of different isoperiodic series (different periods, aromatic and aliphatic, etc.) the values $(\eta)_{P,T}$ (Fig. 1), $(\gamma)_{P,T}$ (Fig. 2) and $(d)_{P,T}$ (Fig. 3) increases linearly with increase in the μ of the molecules. The same is also observed for such y_i ad T_b, T_{crit} and ΔH_{vapor}; for these properties, especially in the case of small molecules, a better compliance with the discussed rule is obtained by taking into account the small differences in the α of the molecules, existing also in the case of isoperiodic compounds, and by not using the values T_b or T_{crit}, but instead $T_b/R_D^{0.5}$ or $T_{crit}/R_D^{0.5}$ (Figs. 4 and 5).

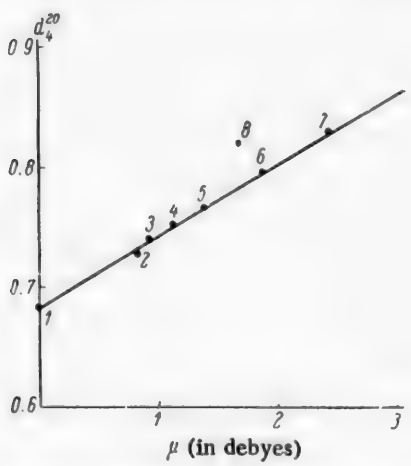

Fig. 3. Dependence of the values of the density d (20°) in isoperiodic series on the dipole moment of the molecules. 1) n-C_7H_{16}; 2) $(C_2H_5)_3N$; 3) (n-C_3H_7)$_2$NH; 4) n-$C_4H_9OC_2H_5$; 5) n-$C_6H_{13}NH_2$; 6) n-$C_6H_{13}F$; 7) n-$C_5H_{11}CHO$; 8) n-$C_6H_{13}OH$.

It is characteristic that the melting point T_m of many members of the same isoperiodic series, but only in the case of small molecules, also increases linearly with increase in μ (Fig. 6).

A series of other experimental data, confirming the character of the discussed relationships, is given in earlier published papers [6-12].

As follows from figures 7 and 8, the values of the dielectric permeability – $(\varepsilon - 1)_{P,T,V}$ (V is the frequency of the external field) in a series of isoperiodic compounds of the first type, in

contrast to the earlier discussed y_i, do not increase linearly with increase in μ, but rather with increase in μ^2, which reflects the influence of μ on ε not only through the number of molecules per unit volume, but also through the orientation polarization. The values of the thermal coefficients $K_d = \frac{1}{d}\frac{\Delta d}{\Delta T}$ and $K_\gamma = \frac{1}{\gamma}\cdot\frac{\Delta\gamma}{\Delta T}$ (Fig. 9) at the same T_2 and T_1 ($\Delta T = T_2 - T_1$) decrease linearly with increase in μ.

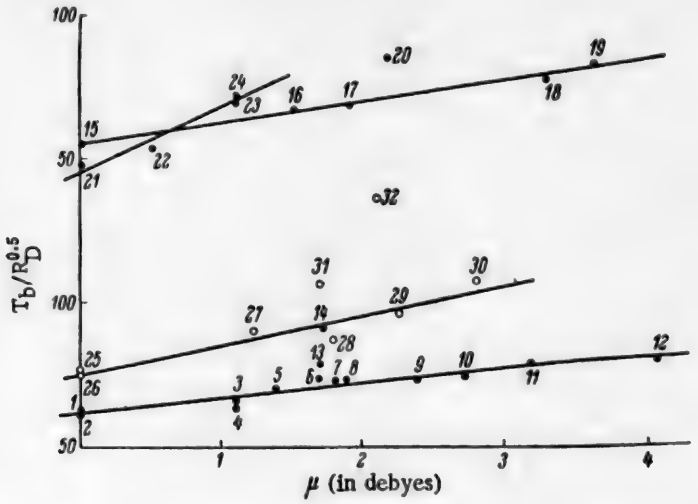

Fig. 4. Change in the values of $T_b/R_D^{0.5}$ in a series of isoperiodic compounds. 1) n-C_6H_{14}; 2) n-$C_4H_9CH = CH_2$; 3) n-$C_4H_9OCH_3$; 4) n-$C_3H_7OC_2H_5$; 5) n-$C_5H_{11}NH_2$; 6) $C_2H_5COOCH_3$; 7) $C_2H_5OCOCH_3$; 8) n-C_3H_7OCOH; 9) n-C_4H_9CHO; 10) $C_2H_5COC_2H_5$; 11) n-$C_3H_7NO_2$; 12) n-C_4H_9CN; 13) n-$C_5H_{11}OH$; 14) n-C_3H_7COOH; 15) $Si(CH_3)_4$; 16) $S(C_2H_5)_2$; 17) n-C_4H_9Cl; 18) C_2H_5NCS; 19) C_2H_5SCN; 20) $Cl(CH_2)_3OH$; 21) SiH_4; 22) PH_3; 23) H_2S; 24) HCl; 25) C_2H_6; 26) C_2H_4; 27) CH_3NH_2; 28) CH_3F; 29) HCHO; 30) HCN; 31) CH_3OH; 32) H_2O_2.

In a series of isoperiodic compounds of the second type for y_i, depending only on the cohesion forces and, consequently, directly independent of m and v_M, and specifically, for example, for T_b and T_{crit} the values $T_b/R_D^{0.5}$ and $T_{crit}/R_D^{0.5}$ also increase almost linearly with increase in the μ of the molecules [12, 13].

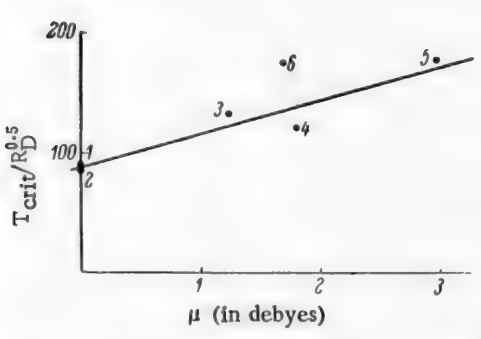

Fig. 5. Dependence of the values of $T_{crit}/R_D^{0.5}$ on the dipole moment of the molecules. 1) C_2H_6; 2) C_2H_4; 3) CH_3NH_2; 4) CH_3F; 5) HCN; 6) CH_3OH.

The above indicates that comparing the values of different y_i in a series of isoperiodic compounds makes it possible, in contrast to comparing the given values of these properties [14], to show in almost pure form (separate from the influence of α) the effect of the dipole-dipole interaction of the molecules. It is manifested in regular manner for all polar substances, and, consequently, there is no reason for separating them into compounds with low and with high values of μ [15]. In accordance with the decrease in the role of the cohesion forces in dipole-dipole interaction with increase in T, the slope of the straight line, reflecting the increase in the values of y_i per ID for such y_i as h, d, γ and ε, decreases; at the same time, the effect of these forces still appears at high T, which follows from the data for T_b and T_{crit}. In harmony with the de-

crease in the polar effect of the dipole group with increase in the length of the hydrocarbon chain [3, 16], the slope of the indicated straight line also decreases with increase in the length of this chain for isoperiodic compounds; at the same time, the effect of dipole-dipole interaction is also manifested for compounds with a substantial polarizability of the remaining portion of the molecules, for example, in the substituted benzene series [15].

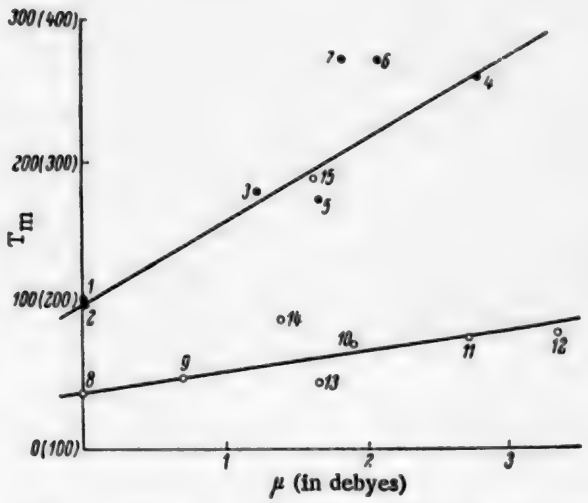

Fig. 6. Change in T_m in a series of isoperiodic compounds. 1) C_2H_6; 2) C_2H_4; 3) CH_3NH_2; 4) HCN; 5) CH_3OH; 6) H_2O_2; 7) NH_2NH_2; 8) n-C_4H_{10}; 9) $(CH_3)_3N$; 10) $HCOOCH_3$; 11) CH_3COCH_3; 12) C_2H_5CN; 13) n-C_3H_7OH; 14) n-$C_3H_7NH_2$; 15) CH_3COOH.

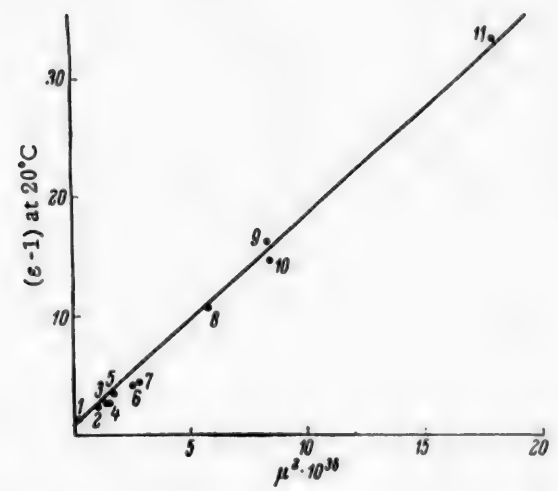

Fig. 8. Change in the values of ε -1 in a series of isoperiodic compounds. 1) n-$C_6H_5H_7$-n; 2) $C_6H_4(OCH_3)CH_3$-o; 3) $C_6H_4(OCH_3)CH_3$-M; 4) $C_6H_4(OCH_3)CH_3$-n; 5) $C_6H_5OC_2H_5$; 6) $C_6H_5N(CH_3)_2$; 7) $C_6H_5NHC_2H_5$; 8) $C_6H_4(OCH_3)OH$-o; 9) $C_6H_4(CHO)OH$-o; 10) $C_6H_5COCH_3$; 11) $C_6H_5NO_2$.

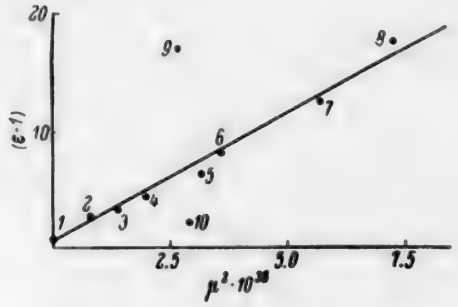

Fig. 7. Change in the values of ε -1 at 20° in a series of isoperiodic compounds. 1) n-C_5H_{12}; 2) $(C_2H_5)_2NH$; 3) $(C_2H_5)_2O$; 4) n-$C_4H_9NH_2$; 5) CH_3COOCH_3; 6) $HCOOC_2H_5$; 7) n-C_3H_7CHO; 8) $C_2H_5COCH_3$; 9) n-C_4H_9OH; 10) C_2H_5COOH.

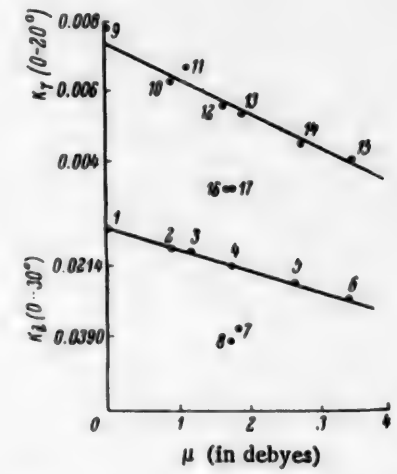

Fig. 9. Change in the values of K_d at 0-30°C and K_γ at 0-20°C in a series of isoperiodic compounds. 1) n-C_5H_{12} (10-30°); 2)$(C_2H_5)_2NH$; 3) $(C_2H_5)_2O$; 4) $HCOOC_2H_5$; 5) $C_2H_5COCH_3$; 6) n-C_3H_7CN; 7) C_2H_5COOH; 8) n-C_4H_9OH(0-20°); 9) n-C_5H_{12} (15-30°); 10) $(C_2H_5)_2NH$ (15-30°); 11) $(C_2H_5)_2O$ (15-30°); 12) CH_3COOCH_3; 13) $HCOOC_2H_5$; 14) $C_2H_5COCH_3$; 15) n-C_3H_7CN; 16) n-C_4H_9OH; 17) C_2H_5COOH.

Obviously, it is impossible to consider valid the assumption that it is possible to neglect in the case of liquids the influence of the polarity of the molecules even at low values of μ [17, 18] or that μ exerts noticeable influence on y_i only during formation due to the dipole interaction of the complexes of the molecules [19].

A proportionality between the y_i values of liquids and the values of μ or μ^2 reflects the total effect of the dipole-dipole interaction on a given y_i, i.e., its effect on the change is not only the cohesion forces between the molecules. Since in a condensed state the dipole-dipole interaction of a given pair of molecules can also be compensated to a certain degree by the same type of interaction with other neighboring molecules or by repulsion forces [20], it is impossible to expect a proportionality between the values of y_i and the values of the energy of interaction of the dipoles of an isolated pair of freely revolving molecules, increasing proportionally to μ^4 [17].

As follows from the graphs, a linear relationship also exists between μ or μ^2 and the members of isoperiodic series, differing from each other in details of shape and containing several polar functional groups in the molecule. Thus, in the disubstituted benzene series, with highly polar functional groups, the different y_i values of the isomers in the liquid state show regular change with the μ values of their molecules as a whole, and not of particular group moments or their sum [21]. Only for such y_i as T_m are substantial deviations from a linear relationship with μ observed for compounds, possessing molecules differing in details of shape and containing several polar groups in the molecule. Apparently, in the liquid state, at temperatures at some distance from T_m, the molecules revolve at a sufficiently rapid rate so that, with small differences in the shape, they behave on the average as particles with the same shape [22] and are separated from each other by distances, where the interaction of the molecules is determined by the moment, characteristic for the molecule as a whole, and not for its individual parts. Consequently, there is no reason to transfer the conclusions regarding the substantial influence of particular dipoles, ensuring from the data for T_m and the solubility of solids [17], to their properties in the liquid state. Some members of isoperiodic series exhibit somewhat high deviations in either direction from a straight line, reflecting the above established relationship between y_i and μ or μ^2. This is associated both with a superimposition of the differences in the details of the shape of molecules and due to the fact that the molecules of the different members of a series do not possess, except for μ, strictly the same remaining properties. The reasons for the greater deviations of the T_b of fluoro derivatives and the $\underline{d}$ of nitriles and ketones of the aliphatic series still remain unexplained. Only the members of the series, made up of the complexes of the molecules, and specifically carboxylic acids, hydroxyl-, and amino-containing compounds, fail to rigidly obey the established relationships. Here the character of the deviations is found to be in accord with the influence of complex-formation on the properties of the particles composing the substances [7, 11-13, 23] and with the influence of the properties of the particles on the values of y_i [11-13]. Since the complexes of molecules possess greater values of m and α than the molecule, the discussed substances in the case of η, T_b and T_{crit} possess considerably greater, and in the case of the thermal coefficients, on the other hand, considerably lower values of the corresponding y_i than follows from the properties of their molecules; to a lesser degree, the $\underline{d}$ and γ values of associated substances deviate toward the side of positive values, since the complex possesses a greater v_M value than the molecule. In the case of ε, where the effect of μ is more sharply manifested, the deciding factor in determining the character of the influence of complex-formation is, obviously, the value of the moment of the complex , and this explains why carboxylic acids (where the μ of the complex is smaller than the μ of the individual molecules) show a negative, and alcohols and phenols (where the μ of the complex is greater than the μ of the molecules) show a positive deviation from a straight line.

Apparently, the reverse relationships are observed in the case of T_m, which is associated with a superimposition of the packing effect of the complexes in the crystal. The indicated complexes in the case of the discussed hydroxyl- and amino-containing compounds are formed as the result of hydrogen bonding between the molecules.

It is specifically for this reason that compounds, containing OH and NHR groups, but forming intramolecular hydrogen bonds (for example, o-hydroxybenzaldehyde, o-nitrophenol, o-nitromethylaniline, etc.) and hence deprived of the possibility to form, to any noticeable degree, complexes of the molecules, obey the rules general for other members of the series and do not show deviations from a straight line (Fig. 8) (see also [7, 8, 10, 11]). The indicated influence of complex-formation and of intramolecular hydrogen bonding is also manifested with T_b and even with T_{crit}, which indicates the high stability of the hydrogen bonds in the case of alcohols and phenols. On the other hand, compliance or a sharp noncompliance of the members of an isoperiodic series, containing functional groups inclined to form hydrogen bonds, with the established relationships can, obviously, serve as a criterion of the presence of bonds of such type inside the molecule or between molecules. Thus, from the above it follows that aliphatic amines and imines are noticeably associated in the solid state, while in the liquid state, in contrast to the aromatic

analogs, they hardly form complexes of the molecules. The established relationships also testify to the need of a strict demarcation of the phenomena of orientation of the molecules due to dipole-dipole interaction and complex-formation due to hydrogen bonding [24].

SUMMARY

1. In the series of isoperiodic compounds the values of the macrophysical properties of substances in the liquid state under the same external conditions show regular change with the dipole moment of the molecules.

2. The established relationships between various macrophysical properties of substances and the dipole moment of the molecules in a series of isoperiodic compounds can serve as a criterion of the presence in the liquid state of complexes of the molecules or of intramolecular hydrogen bonding in the molecule.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

CHANGES IN THE PROPERTIES OF SUBSTANCES IN DIFFERENT SERIES OF CHEMICAL COMPOUNDS

IV. SERIES OF SUBSTITUTED DERIVATIVES

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Original article submitted June 13, 1960

The influence of a functional group X on such properties as the dipole moment, vibration frequency, chemical reactivity, etc. of molecules of composition RX (where R = H, alkyl, or aryl, and the X group consists of the atoms of different periods and groups of the periodic system) is subjected to exhaustive examination in the literature. The situation is different on the score of the influence exerted by the introduction of these groups into RH on the macrophysical properties of substances y_i; density (d), friction coefficient (η), surface tension (γ), boiling point (T_b), melting point (T_m), critical temperature ($T_{cr.}$), dielectric permeability (ε), etc. Repeated consideration of this problem in the past [1, 2] reduced to introducing specific increments or decrements into various additive schemes of different y_i for each X or its component atoms (bonds). Since the mutual influence (conjugation, inductive and steric interaction) of the atoms and groups in the molecule lead to the situation that the properties of X itself, as well as its effect on the properties of the molecule as a whole, depend on the remaining portion of the molecule, then increments and decrements of such type, in addition to their physical vagueness, can be applied only to a limited range of compounds.

Obviously, a more rational approach is not to attempt to link the effect of X on the value of some y_i directly with the composition and structure of the group in question, but instead an attempt should be made to link this effect with the changes in such properties of molecules as size v_M, shape f, polarizability α, mass m, and dipole moment μ, caused by the introduction of X into RH. Actually, by applying to the series of substituted derivatives the relationships established earlier for a homologous series and the series of isogroup and isoperiodic compounds [3], it proves possible to obtain relationships between $(y_i)_{P,T}$ and the properties of molecules that are general for extremely different series of RX (with R = H, C_nH_{2n+1}, C_6H_5, etc.).

Thus, from figure 1 it can be seen that the term $\left(\frac{\eta}{M^{1/2}R_D^{3/2}}\right)_{P,T}$ (M is the molecular weight, and R_D is the molecular refraction) in a series of substituted derivatives of composition n-C_4H_9X shows approximately linear increase with the μ of the molecules, in which connection the origin of the straight line coincides with the value of $\left(\frac{\eta}{M^{1/2}R_D^{3/2}}\right)_{P,T}$ for the corresponding RH, i.e., the member in the series with $\mu = 0$.

In all the series of substituted derivatives, a linear relationship also exists between μ and the values plotted as the ordinates in figures 2-6. A series of data, supporting these relationships, is also given in previously published papers [4-8]. In the series of substituted derivatives the values $\left[(\varepsilon - 1)\frac{(v_M \cdot 10^{24})^{3/2}}{R_D}\right]_T$ increase proportionally to μ^2 (Figs. 7 and 8).

As can be seen from the graphs, most of the members in the series, with several different details of the shape of the molecules and several group moments in the substituent X, satisfactorily obey the established relationships. This supports the theory [3] that in the liquid state (for small molecules this is also true for T_m) (Fig. 6) the details of the shape of the molecules exert little influence on the character of the changes in y_i with change in the moment of the molecules and that in this state the value $(y_i)_{P,T}$ is determined in the final analysis by the moment of the molecule as a whole, and not by the partial moments of the individual groups [9]. For some members in a series of substituted derivatives and only for individual y_i is a somewhat greater than usual noncompliance with the established relationships observed (for example, in the case of the d of halo-substituted aromatic derivatives or the

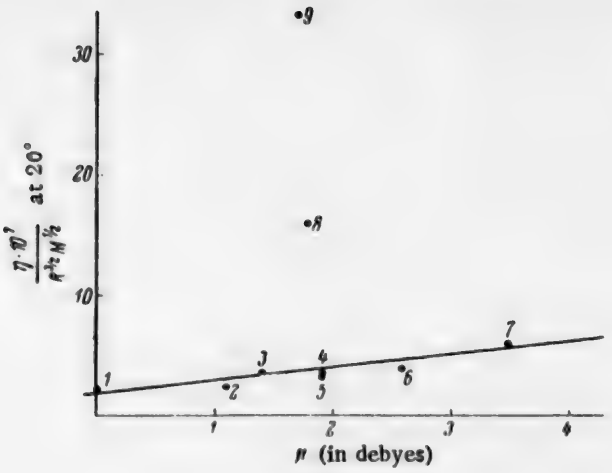

Fig. 1. Change in the values of $\frac{\eta \cdot 10^7}{R_D^3 M^{1/2}}$ in a series of substituted derivatives of composition $-C_4H_9X$ at 20°. Value of X: 1) CH_3; 2) OC_2H_5; 3) SH; 4) Cl(Br); 5) $COOC_2H_5$; 6) $COCH_3$; 7) CN; 8) COOH; 9) OH.

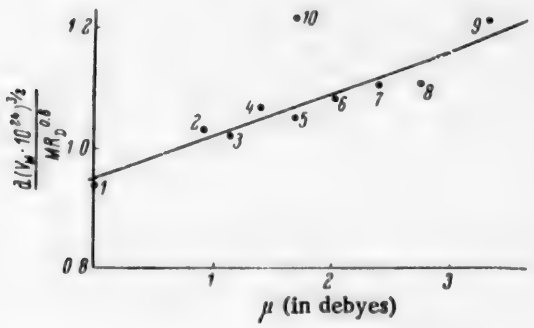

Fig. 2. Dependence of the values of $\frac{d\,(v_M \cdot 10^{24})^{2/3}}{M R_D^{0.6}}$ in a series of substituted derivatives of composition C_2H_5X on the dipole moment of the molecules. Value of X: 1) $n\text{-}C_3H_7$; 2) NHC_2H_5; 3) OC_2H_5; 4) SH; 5) I; 6) Cl; 7) CHO; 8) $COCH_3$; 9) CN; 10) OH.

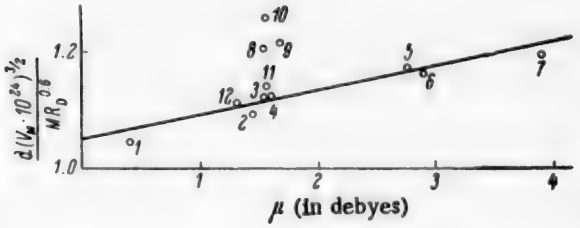

Fig. 3. Dependence of the values of $\frac{d\,(v_M \cdot 10^{24})^{2/3}}{M R_D^{0.6}}$ in a series of substituted derivatives of composition C_6H_5X on the dipole moment of the molecules. Value of X: 1) C_2H_5; 2) F; 3) Br; 4) $N(CH_3)_2$; 5) $COCH_3$; 6) CHO; 7) CN; 8) NH_2; 9) CH_2OH; 10) OH; 11) Cl; 12) I.

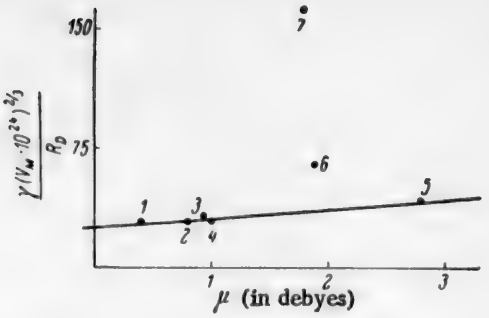

Fig. 4. Change in the values of $\frac{\gamma (v_M \cdot 10^{24})^{2/3}}{R_D}$ in a series of substituted derivatives of composition HX at -181°. Value of X: 1) I; 2) 2) Br; 3) SH; 4) Cl; 5) CN; 6) F; 7) OH.

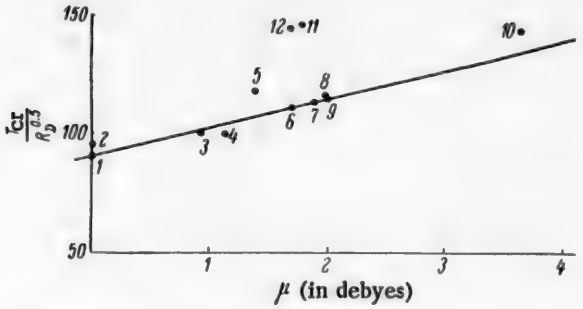

Fig. 5. Dependence of $T_{cr}/R_D^{0.5}$ in a series of substituted derivatives of composition C_2H_5X on the dipole moment of the molecules. Value of X: 1) H; 2) n-C_3H_7; 3) NHC_2H_5; 4) OC_2H_5; 5) SH; 6) $OCOCH_3$; 7) I; 8) Br; 9) Cl; 10) CN; 11) COOH; 12) OH.

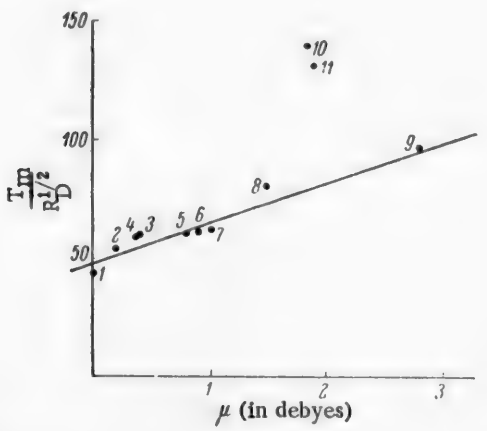

Fig. 6. Change in the values of $T_m/R_D^{0.5}$ in a series of substituted derivatives of composition HX. Value of X: 1) CH_3; 2) TeH; 3) SeH; 4) I; 5) Br; 6) SH; 7) Cl; 8) NH_2; 9) CN; 10) OH; 11) F.

η of fluoro-substituted derivatives), which could be due either to inaccuracies in determining the values of both y_i and the properties of the molecules, or to some inaccuracy in the value adopted for the α-exponent.

Only the members of all of the series of substituted derivatives where X contains OH, NH_2, or COOH, i.e., the compounds composed of molecular complexes, formed as the result of hydrogen bonding between the molecules, fail to rigidly obey the established relationships for all y_i. Here, in accordance with the properties of the formed complexes, in the case of ε the value of $(\varepsilon - 1)\frac{(v_M \cdot 10^{24})^{1.5}}{R_D}$ for acids lies below, and that for alcohols and phenols lies above the straight line, reflecting the dependence of this value on μ^2 (Figs. 7 and 8); in the case of other y_i, for which the effect of μ is smaller, all of the compounds of the discussed type show a noticeable deviation toward higher values of the corresponding terms. The data for the changes in y_i in the series of substituted derivatives confirm [3] the fact that in the liquid state, aliphatic amines, in contrast to the aromatic analogs, behave like substances that are almost devoid of the indicated complexes; in the solid state they are apparently strongly associated.

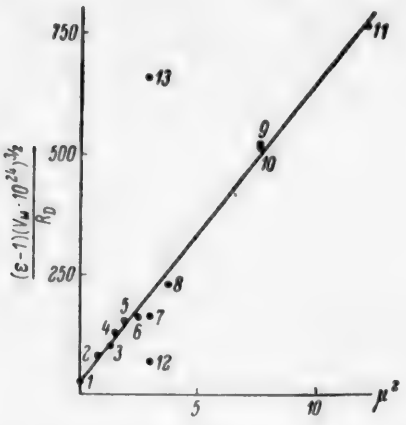

Fig. 7. Dependence of the $\frac{(\varepsilon - 1)(v_M 10^{24})^{2/3}}{R_D}$ of substituted derivatives of composition C_2H_5X on the square of the dipole moment of the molecules at 20°. Value of X: 1) n-C_3H_7; 2) NHC_2H_5; 3) OC_2H_5; 4) NH_2; 5) SH; 6) SC_2H_5; 7) $COOC_2H_5$; 8) HCOO; 9) $COCH_3$; 10) COC_2H_5; 11) CN; 12) COOH; 13) OH.

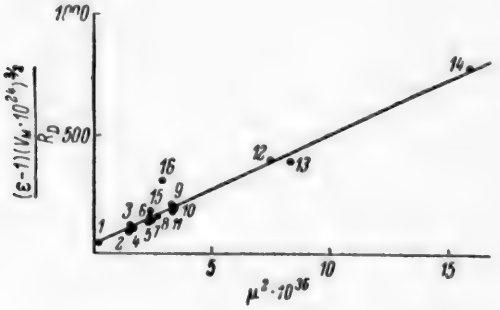

Fig. 8. Dependence of the $\frac{(\varepsilon - 1)(v_M 10^{24})^{2/3}}{R_D}$ of substituted derivatives of composition C_6H_5X on the square of the dipole moment of the molecules at 20°. Value of X: 1) CH_3; 2) OCH_3; 3) OC_2H_5; 4) I; 5) Br; 6) Cl; 7) $N(CH_3)_2$; 8) $NHCH_3$; 9) $COOCH_3$; 10) $COOC_2H_5$; 11) CH_2Cl; 12) CHO; 13) $COCH_3$; 14) CN; 15) NH_2; 16) CH_2OH.

The fact that the values of highly different macrophysical properties of substances in the liquid state in the series of substituted derivatives obey the same functions of the properties of molecules as in the homologous series and the series of isogroup and isoperiodic compounds supports the validity of the theory that it is possible to express the complex influence of each of the properties of molecules on a given y_i through the total effect of these properties of molecules as a whole. Here, for molecules with the same or nearly the same shape, the total effect of each of the properties of molecules is independent of each other, except α, the total effect of which is different for polar and nonpolar substances. Total functions of such types disclose general reasons [9] for the differences in the $(y_i)_{X_{ext.}}$ values (X_{ext} = external conditions), and also the rules of their changes in different series of chemical compounds; as a rule, they permit within the limits of the same series of compounds to calculate with sufficient accuracy from the properties of the molecules the values of different $(y_i)_{X_{ext.}}$, and to go from the values of a given $(y_i)_{X_{ext.}}$ of a member in one type of series to a like member in another type of series. Since the discussed functions do not disclose the mechanism of the influence of different properties of molecules on a given $(y_i)_{X_{ext.}}$, but reflect only the total effect under constant external conditions and shape of the molecules, the constant contained in them cannot have a definite physical meaning.

SUMMARY

1. Semiempirical rules were established for the changes in different macrophysical properties of substances in the liquid state in various series of substituted derivatives of composition RX (where R = H, C_nH_{2n+1}, C_6H_5) with change in the properties of their molecules.

2. The presence of functions, reflecting the total effect of different properties of molecules on various macrophysical properties of substances in the liquid state, and the possibility of their wide application, was shown.

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N,N',N''-TRIETHYLENETRIAMIDOPHOSPHAZO COMPOUNDS AND N',N'',N'''-TRIETHYLENE-N-DIAMIDOPHOSPHINYL-ARENEAMIDINES

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Original article submitted June 9, 1960

Many N-ethylenamides of phosphoric acid [1], acylamidophosphoric acids [2] and arylamidophosphoric acids [3] possess well-defined antiblastic properties, and some of them, for example, TEF and TIOTEF, have found practical use as medicinals [4]. For this reason it seemed of interest to obtain the N-ethylene derivatives of triamidophosphazo compounds, which by their nature are derivatives of an acyliminotriamidophosphoric acid and, consequently, represent acylimino derivatives of TEF. Antiblastic properties are also possessed by some other compounds, in the molecules of which the ethylenamino group is attached to a carbon atom [5], and for this reason it was interesting to obtain the N-ethylene derivatives of N-diamidophosphinylamidines, since the molecules of these compounds contain ethylenamine groups that are attached to both phosphorus and carbon atoms.

N,N',N''-Triethylenetriamidophosphazoacyls (I), N,N',N''-triethylenetriamidophosphazosulfonylaryls (II) and N',N'',N'''-triethylene-N-diamidophosphinylareneamidines (III) are obtained in satisfactory yields by reacting the appropriate chlorides with ethylenimine in the presence of triethylamine.

$$RCON{=}PCl_3 + 3HN(CH_2)_2 \xrightarrow{3Et_3N} RCON{=}P[N(CH_2)_2]_3 \quad (I)$$

$$RSO_2N{=}PCl_3 + 3HN(CH_2)_2 \xrightarrow{3Et_3N} RSO_2N{=}P[N(CH_2)_2]_3 \quad (II)$$

$$RC(=NPOCl_2)Cl + 3HN(CH_2)_2 \xrightarrow{3Et_3N} RC[=NPO[N(CH_2)_2]_2]N(CH_2)_2 \quad (III)$$

The reaction of ethylenimine with N-diphenoxyphosphinyliminobenzoyl chloride in the presence of triethylamine gave N-ethylene-N'-diphenoxyphosphinylbenzamidine (IV).

$$C_6H_5C[=NPO(OC_6H_5)_2]Cl + HN(CH_2)_2 \xrightarrow{Et_3N} C_6H_5C[=NPO(OC_6H_5)_2]N(CH_2)_2 \quad (IV)$$

In all cases the reaction was run in benzene solution at 5-7°. All of the (I), (II) and (III) compounds, with the exception of the readily crystallizing nitro derivatives, separate as viscous oils, which only after long standing under a layer of petroleum ether or ether are converted into comparatively low-melting crystalline compounds (Table). Compound (IV) is a liquid. The (I) and (III) products are much more soluble in water (with the exception of the nitro derivatives) than the (II) products (see table). The ethylenamides melt without decomposition, and their water solutions are neutral (pH ~ 7). Hardly any hydrolysis takes place when neutral water solutions of the ethylenamides are evaporated in vacuo at 20°—the solid residue remaining after evaporation melts only 2-3° below the pure compounds. The ethylenamides are rapidly decomposed in acid aqueous solutions.

The antiblastic properties of the obtained ethylenamides will be the subject of a separate paper.

As starting substances we synthesized by known procedures [6] the previously unknown trichlorophosphazo-o-bromobenzoyl and N-dichlorophosphinyl-p-bromoiminobenzoyl chloride.

EXPERIMENTAL

General procedure for the preparation of compounds (I), (II), (III), and (IV). With vigorous stirring and cooling, a solution of 0.01 g-mole of the appropriate chloride in 50-100 ml of benzene was added to a solution of 0.031 g mole

Ar	Yield (in %)	Melting point	Crystal form and recrystallization solvent	Found (%)
			N,N',N"-Triethylenetriamidophosphazoacyls	
C_6H_5	82	57—58°	Prisms, ether	N 19.37, 19.87 C 56.50, 55.77 H 6.20, 6.18
o-ClC_6H_4	88	85—87	Needles, ether	N 17.77
p-ClC_6H_4	85	72—74	Prisms, ether	N 18.22
o-BrC_6H_4	82	92—94	Prisms, benzene	N 15.43, 16.19
p-BrC_6H_4	90	80—82	Prisms, benzene + petroleum ether + ether (1 : 1 : 1)	N 15.8
m-$NO_2C_6H_4$	82	80—82	Prisms, ether	N 21.10, 22.64
p-$NO_2C_6H_4$	95	97—99	Prisms, benzene	N 22.10
			N,N',N"-Triethylenetriamidophosphazosulfonyl-	
C_6H_5	79	96—98	Prisms, benzene	N 18.53, 17.27
p-$CH_3C_6H_4$	88	108—110	Prisms, benzene	N 17.19, 17.39
p-ClC_6H_4	87	107—109	Clusters of prisms, benzene + petroleum ether (1 : 1)	N 16.54
p-$NO_2C_6H_4$	75	146—148**	Prisms, benzene	N 19.81, C 41.03, H 4.60
			N',N",N"'-Triethylene-N-diamidophosphinyl-	
C_6H_5	77	78—80	Prisms, benzene + petroleum ether (1 : 1)	N 19.18, 19.68, C 56.08, H 6.04
p-ClC_6H_4	89	78—80	Prisms, ether + benzene + petroleum ether (1 : 1 : 1)	N 17.91
p-BrC_6H_4	80	92—93	Prisms, ether + benzene (1 : 1)	N 15.83
			N-Ethylene-N'-diphenoxyphosphinyl	
C_6H_5	89	Liquid	Liquid	N 7.98, 7.31

* ‡ Easily soluble at 20°; + easily soluble at the boiling point; −difficultly soluble at the boiling point; = insoluble at the boiling point.

** When the capillary is introduced into the medium at 100° and then heated rapidly. When heated slowly the compound does not melt up to 230°.

of ethylenimine and 0.031 g mole of triethylamine in 35-40 ml of benzene at such a rate that the temperature remained between 5 and 7°. After adding all of the chloride (20-25 min) the reaction mixture was stirred for another 1-2 hr at room temperature and then it was allowed to stand for 12-14 hr. The precipitate of triethylamine hydrochloride was suction-filtered and the benzene was vacuum-distilled. The residue was either a clear viscous liquid or (in the case of the nitro compounds) a dense crystalline mass. Some of the nitro derivatives coprecipitated with the triethylamine hydrochloride. In these cases they were extracted with boiling benzene. The solid products were washed with petroleum ether (2 x 5 ml), dried, and recrystallized. The water-insoluble ethylenamides (II and the nitro derivatives) were washed with water, then with alcohol, and dried rapidly in vacuo over KOH. The liquid products, after digesting 2-3 times with petroleum ether (10-15 ml) and rubbing with a glass rod, slowly crystallized. The crystals were suction-filtered, washed with petroleum ether or ether, dried, and recrystallized.

Trichlorophosphazo-o-bromobenzoyl. A mixture of 0.2 g mole of o-bromobenzamide, 0.2 g mole of phosphorus pentachloride and 60-80 ml of carbon tetrachloride was heated at 70-75° until the evolution of hydrogen chloride had ceased completely (15-20 min). The carbon tetrachloride was vacuum-distilled at 40°, and the solid

Empirical formula	Calculated (%)	Solubility*				
		water	alcohol	ether	benzene	petroleum ether
ArCON = $P[N(CH_2)_2]_3$ (I)						
$C_{13}H_{17}ON_4P$	N 20.28, C 56.53, H 6.19	+ +	+ +	−	+ +	=
$C_{13}H_{16}ON_4PCl$	N 18.03	+ +	+ +	−	+ +	−
$C_{13}H_{16}ON_4PCl$	N 18.03	+ +	+ +	−	+ +	=
$C_{13}H_{16}ON_4PBr$	N 15.78	−	+ +	+	+ +	−
$C_{13}H_{16}ON_4PBr$	N 15.78	+	+ +	−	+ +	=
$C_{13}H_{16}O_3N_5P$	N 21.80	=	+	+	+	=
$C_{13}H_{16}O_3N_5P$	N 21.80	=	+	+	+	=
aryls $ArSO_2N = P[N(CH_2)_2]_3$ (II)						
$C_{12}H_{17}O_2N_4SP$	N 17.94	=	+	+	+ +	=
$C_{13}H_{19}O_2N_4SP$	N 17.17	−	+ +	+	+ +	−
$C_{12}H_{16}O_2N_4SPCl$	N 16.15	=	+	+	+	=
$C_{12}H_{16}O_4N_5SP$	N 19.64, C 40.34, H 4.50	=	−	−	+	=
areneamidines $ArC\{ = NPO[N(CH_2)_2]_2\} N(CH_2)_2$ (III)						
$C_{13}H_{17}ON_4P$	N 20.28, C 56.53, H 6.19	+ +	+ +	+	+ +	−
$C_{13}H_{16}ON_4PCl$	N 18.03	−	+	+	+ +	=
$C_{13}H_{16}ON_4PBr$	N 15.78	+ +	+ +	+	+ +	=
benzamidine $C_6H_5C[= NPO(OC_6H_5)_2]N(CH_2)_2$ (IV)						
$C_{12}H_{19}O_3N_2P$	N 7.40	−	+	+	+ +	=

residue was recrystallized from petroleum ether. Trichlorophosphazo-o-bromobenzoyl is a colorless crystalline substance, readily soluble in benzene, carbon tetrachloride, ether and acetone, and difficultly soluble in petroleum ether. It crystallizes from petroleum ether as coarse prisms with m.p. 41-43°.

Found equiv. after hydrolysis 4.95, 5.03. $C_7H_4ONPCl_3Br$. Calculated equiv. after hydrolysis 5.00.

N-Dichlorophosphinyl-p-bromoiminobenzoyl chloride was obtained by heating a mixture of equimolecular amounts of p-bromobenzoylamidophosphoryl dichloride and phosphorus pentachloride until the evolution of hydrogen chloride ceased (20 min). The yield was theoretical. N-Dichlorophosphinyl-p-bromoiminobenzoyl chloride is a colorless liquid, readily soluble in benzene, acetone and carbon tetrachloride, and difficultly soluble in petroleum ether and ether.

Found equiv. after hydrolysis 4.89, 4.95. $C_7H_4ONPCl_3Br$. Calculated equiv. after hydrolysis 5.00.

SUMMARY

N,N',N"-Triethylenetriamidophosphazoacyls, N,N',N"-triethylenetriamidophosphazosulfonylaryls and N',N",N"'-triethylene-N-diamidophosphinylareneamidines were obtained by reacting ethylenimine with the appropriate chlorides in the presence of triethylamine.

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HEAT CLEAVAGE OF THE PHENYL ESTER OF TRICHLORO-PHOSPHAZOCARBONIC ACID

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Two directions of heat cleavage are known for phosphazoacyl compounds of type $XCON = PCl_3$. If X is aryl or alkyl, then the cleavage of phosphorus oxychloride occurs and nitriles are formed [1].

$$ArCON{=}PCl_3 \longrightarrow POCl_3 + ArCN \quad (1)$$

If X is alkoxyl, then the oxygen atom migrates to the phosphorus, and the corresponding alkyl halide and isocyanatophosphoryl dichloride are formed in nearly quantitative yield [2].

$$ROCON{=}PCl_3 \longrightarrow RCl + OCNPOCl_2 \quad (2)$$

It seemed of interest to determine the manner in which the aromatic esters of trichlorophosphazocarbonic acid are cleaved on heating, since for them cleavage in accordance with scheme 2 is not very probable, due to the fact that the linkage of oxygen to the aromatic ring is ruptured with great difficulty.

The phenyl ester of trichlorophosphazocarbonic acid was obtained from phenylurethan and phosphorus pentachloride (see [3]).

$$C_6H_5OCONH_2 + PCl_5 \longrightarrow 2HCl + C_6H_5OCON{=}PCl_3$$

The reaction goes quantitatively, but at a higher temperature and a considerably slower rate than for the alkylurethans [2, 3]. The phenyl ester of trichlorophosphazocarbonic acid is a colorless, viscous liquid with a sharp odor, and is easily hydrolyzed by atmospheric moisture. When treated with 1 g mole of formic acid or water this compound is converted in quantitative yield to phenylurethan-N-phosphoryl dichloride $C_6H_5OCONHPOCl_2$, identical with the product obtained by the addition of phenol to isocyanatophosphoryl dichloride [4], which proves its structure.

When heated, the phenyl ester of trichlorophosphazocarbonic acid is decomposed just as easily as the alkyl esters of trichlorophosphazocarbonic acid. Short heating up to 80° causes complete cleavage of the compound, but here the process goes simultaneously in two directions, as a result of which a mixture of products is formed, from which we were able to isolate 19.3% of phosphorus oxychloride, 43.7% of the triphenyl ester of cyanuric acid, 46.7% of monophenylphosphoryl dichloride, and 37.9% of cyanuric chloride.

The formation of phosphorus oxychloride and triphenyl cyanurate proves that the heat cleavage of the phenyl ester goes by a scheme that is analogous to scheme (1).

$$C_6H_5OCON{=}PCl_3 \longrightarrow POCl_3 + (C_6H_5OCN) \longrightarrow \frac{1}{3}\,C_3N_3(OC_6H_5)_3$$

The initially formed phenyl ester of cyanic acid is immediately trimerized to the triphenyl ester of cyanuric acid.

The formation of cyanuric chloride and monophenylphosphoryl dichloride is explained by the fact that at first the phenyl ester is isomerized to phenoxydichlorophosphazocarbonyl chloride, which immediately decomposes by

a scheme analogous to (1), with the cleavage of monophenylphosphoryl dichloride and the formation of cyanogen chloride, which polymerizes to cyanuric chloride.

$$C_6H_5OCON{=}PCl_3 \longrightarrow [ClCON{=}P(OC_6H_5)Cl_2] \longrightarrow C_6H_5OPOCl_2 + \frac{1}{3}C_3N_3Cl_3$$

The yields of the heat cleavage products (see above) show that when the phenyl ester is slowly heated in vacuo the cleavage goes at approximately the same rate in both directions.

Neither chlorobenzene nor isocyanatophosphoryl dichloride could be found among the cleavage products; consequently, as was to be expected, the heat cleavage of the phenyl ester of trichlorophosphazocarbonic acid does not take place in accordance with scheme 2.

EXPERIMENTAL

Phenyl ester of trichlorophosphazocarbonic acid. A mixture of 0.3 g mole of phenylurethan, 0.3 g mole of phosphorus pentachloride and 20 ml of carbon tetrachloride was heated, with stirring, in an oil bath at 50-60° until the evolution of hydrogen chloride ceased (1-1.5 hr). The carbon tetrachloride was vacuum-distilled at 30°; the residue, a clear viscous liquid, was the phenyl ester of trichlorophosphazocarbonic acid. The yield was quantitative.

Found equiv. after hydrolysis 4.94, 4.96. $C_7H_5O_2NPCl_3$. Calculated equiv. after hydrolysis 5.00.

Phenylurethan-N-phosphoryl dichloride. With vigorous stirring, under the conditions described earlier for the preparation of alkylurethan-N-phosphoryl dichlorides [3], 0.1 g mole of formic acid or 0.1 g mole of water was slowly added to a mixture of 0.1 g mole of the phenyl ester of trichlorophosphazocarbonic acid and 50 ml of carbon tetrachloride. The yield of the dichloride was nearly quantitative, and it was identified by the mixed melting point [4] and by titration.

Found equiv. after hydrolysis 3.93, 3.92. $C_7H_6O_3NPCl_2$. Calculated equiv. after hydrolysis 4.00.

Heat cleavage of phenyl ester of trichlorophosphazocarbonic acid. The phenyl ester of trichlorophosphazocarbonic acid was heated at 80° for 15 min. Here gas bubbles were evolved, and the liquid became more fluid. After cooling, an equivalent amount of anhydrous formic acid was added. Neither by standing nor by treatment with solvents could the dichloride of phenylurethan-N-phosphoric acid be isolated. This shows that the phenyl ester of trichlorophosphazocarbonic acid decompose completely when heated, since when it is treated with formic acid it is converted quantitatively to the stable and readily crystallizing dichloride of phenylurethan-N-phosphoric acid (see above).

The heat cleavage of the phenyl ester of trichlorophosphazocarbonic acid was run under highly varied conditions. In all cases we were able to isolate only four pure compounds from the reaction mixture (see below). The best results were obtained when the cleavage was conducted in vacuo. The experimental conditions giving the best yields are described.

Into a Claisen flask, connected to a receiver, and cooled to -80°, was charged 0.1 g mole of the phenyl ester of trichlorophosphazocarbonic acid. The decomposition was conducted in vacuo (5 mm), heating the flask gradually in an oil bath. Distillation began at 75° (bath temperature 110°) and was ended at 150° (bath temperature 200°) in 1.5 hr. The following fractions were obtained: up to 120°–25 g, 120-150°–24 g, residue in the flask, 5 g. The following compounds were isolated from these fractions by fractional distillation and recrystallization.

Phosphorus oxychloride, 19.3%, identified by the boiling point and the melting point.

Triphenyl ester of cyanuric acid, 43.7%, after recrystallization from alcohol, m.p. 222-224°, which corresponds to the literature data [5].

Cyanuric chloride, 37.9%, m.p. 145-147°, which corresponds to the literature data [6]. For identification, the cyanuric chloride was converted to cyanuric acid by treatment with water.

Found %: N 32.49, 32.60. $C_3H_3O_3N_3$. Calculated %: N 32.35.

Monophenylphosphoryl dichloride, 46.7%, b.p. 249-250°, which corresponds to the literature data [7].

Found %: Cl 32.82, 32.79. Equiv. after hydrolysis 3.87, 3.90. $C_6H_5O_2PCl_2$. Calculated %: Cl 33.64. Equiv. after hydrolysis 4.00.

For identification, the monophenylphosphoryl dichloride was reacted with aniline to give the crystalline dianilidomonophenyl phosphate, which in turn was identified by the mixed melting point with the authentic dianilide [8].

SUMMARY

1. Phenylurethan reacts with phosphorus pentachloride in accordance with the general scheme of the phosphazo reaction.

2. When heated, the phenyl ester of trichlorophosphazocarbonic acid undergoes cleavage in two directions with the formation of phosphorus oxychloride and triphenyl cyanurate in one case, and of monophenylphosphoryl dichloride and cyanuric chloride in the other.

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ESTERS OF URETHANPHOSPHORIC ACIDS. II

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The dimethyl ester of methylurethan-N-phosphoric acid ("Kiev 20-35" compound) and the dimethyl ester of isopropylurethan-N-phosphoric acid ("Avenin") are active systemic insecticides which are practically completely non-toxic to warm-blooded animals [1]. Both were prepared by starting with methylurethan and proceding by way of the methyl ester of trichlorophosphazocarbonic acid [2]. The latter is not entirely suited for use under factory conditions since, if it is carelessly heated, it decomposes violently and gives off large quantities of gas which may lead to unfortunate results. Therefore it was decided to work out a method of producing "K-20-35" that would avoid the step in which the methyl ester of trichlorophosphazocarbonic acid is formed.

The phosphazo reaction proceeds with the absorption of a large amount of heat. When 0.1 g mole of methylurethan reacts with 0.1 g mole of PCl_5 and the external air temperature is +20°, the temperature of the reaction mixture drops to -20°. The isomerization reaction and the splitting off of the esters of trichlorophosphazocarbonic acid are exothermic. If these two processes are carried out simultaneously, the over-all heat balance is negative. In this way, by carrying out the reaction of methylurethan with phosphorus pentachloride at a temperature higher than the decomposition temperature of the methyl ester of trichlorophosphazocarbonic acid, it is possible to prepare the chloride of isocyanatophosphoric acid in one step in any quantity entirely without danger, thus avoiding the step of preparing the methyl ester of trichlorophosphazocarbonic acid with its danger of explosion.

$$NH_2COOCH_3 + PCl_5 \longrightarrow Cl_2PONCO + 2HCl + CH_3Cl$$

It was found previously that alcohols combine quantitatively with the dichlorides of isocyanatophosphoric acid and form the dichlorides of urethan-N-phosphoric acids which, by treatment with alcohols, form the diesters of urethan-N-phosphoric acids in high yields [3]. Thus this scheme is completely suitable for the factory production of "K-20-35" and "Avenin."

In the preparation of "K-20-35" or "Avenin" it is most convenient to start with phosphorus trichloride which is mixed with a suitable solvent (carbon tetrachloride, dichloroethane, chlorobenzene). The mixture is saturated with chlorine, heated to 80° and this temperature maintained (the bulb of the thermometer in the reaction mixture). While the mixture is stirred vigorously, melted methyl- or ethylurethan is added and the rate of addition and the external heating are regulated so that the temperature of the mixture is maintained within the limits of 70-80°. Subsequent processing is in accordance with previously described methods [2, 4].

A number of diesters of urethan-N-phosphoric acids, not previously described in the literature, were prepared for the purpose of studying their insecticidal properties.

$$Cl_2PONCO \xrightarrow[+ROH]{} Cl_2PONHCOOR \xrightarrow[+2R'OH]{} (R'O)_2PONHCOOR$$

The diesters of urethan-N-phosphoric acids are colorless, crystalline substances (Table 1), which are easily soluble in benzene and alcohol, but only slightly soluble in petroleum ether. The dialkyl ester of p-nitrophenylurethan-N-phosphoric acid are liquids. The chemical properties of the diesters of urethan-N-phosphoric acids, described in the present paper, are close to the chemical properties of the diesters of urethan-N-phosphoric acids described previously [2, 4]. All the diesters described in the paper have weaker insecticidal properties than "K-20-35" and "Avenin."

TABLE 1. Diesters of Urethan-N-Phosphoric Acids – ROCONHPO(OR')$_2$ *

Compound number	R	R'	Yield (in %)	M. p.	% N found	Empirical formula	% N calculated
1	iso-C_3H_7	iso.-C_3H_7	50	128—129°	5.69, 5.64	$C_{10}H_{22}O_5NP$	5.24
2	$NC(CH_3)_2C$	CH_3	50	75—76	12.10, 12.22	$C_7H_{13}O_5N_2P$	11.86
3	$NC(CH_3)_2C$	iso -C_3H_7	70	168—170	9.31, 9.28	$C_{11}H_{21}O_5N_2P$	9.59
4	cyclo.-C_6H_{11}	CH_3	70	Liquid	5.72, 5.68	$C_9H_{18}O_5NP$	5.57
5	C_6H_5	CH_3	50	78—80	5.64, 5.61	$C_9H_{12}O_5NP$	5.71
6	C_6H_5	C_2H_5	50	124—126	5.00, 5.05	$C_{11}H_{16}O_5NP$	5.12
7	C_6H_5	iso -C_3H_7	52	122—123	5.10, 4.99	$C_{13}H_{20}O_5NP$	4.65
8	C_6H_5	$NC(CH_3)_2C$	52	178—180	12.22, 12.15	$C_{15}H_{18}O_5N_3P$	11.68
9	C_6H_5	$C_6H_5CH_2$	60	124—126	3.21, 3.39	$C_{21}H_{20}O_5NP$	3.52
10	C_6H_5	cyclo-C_6H_{11}	45	111—113	4.10, 3.99	$C_{19}H_{28}O_5NP$	3.70
11	C_6H_5	C_6H_5	60	121—123	4.16, 4.20	$C_{19}H_{16}O_5NP$	3.79
12	C_6H_5	p-$NO_2C_6H_4$	50	149—150	8.78, 8.89	$C_{19}H_{14}O_9N_3P$	9.15
13	2-CH_3,5-$(CH_3)_2CHC_6H_3$	CH_3	75	110—112	4.60, 4.63	$C_{13}H_{20}O_5NP$	4.65
14	2-CH_3,5-$(CH_3)_2CHC_6H_3$	iso-C_3H_7	75	131—132	3.57, 3.59	$C_{17}H_{28}O_5NP$	3.92
15	p HOC_6H_4	CH_3	70	121—124	4.98, 4.99	$C_9H_{12}O_6NP$	5.36
16	o-$NO_2C_6H_4$	CH_3	68	54—56	9.69, 9.77	$C_9H_{11}O_7N_2P$	9.65
17	p-$NO_2C_6H_4$	CH_3	60	Liquid	9.32, 9.41	$C_9H_{11}O_7N_2P$	9.65
18	p-$NO_2C_6H_4$	C_2H_5	50	Liquid	8.60, 8.50	$C_{11}H_{15}O_7N_2P$	8·80
19	p-$NO_2C_6H_4$	iso-C_3H_7	50	Liquid	8.72, 8.68	$C_{13}H_{19}O_7N_2P$	8.10
20	p-$NO_2C_6H_4$	$C_6H_5CH_2$	60	124—126	6.31, 6.70	$C_{21}H_{19}O_7N_2P$	6.33
21	p-$NO_2C_6H_4$	p-$NO_2C_6H_4$	60	114—115	10.96, 10.85	$C_{19}H_{13}O_{11}N_4P$	11.11

* Compounds 1,4,5,6 and 7 give prism-shaped crystals from alcohol. Compounds 2,3 and 8-15 yield a fine crystalline powder from dichloroethane. Compounds 16, 20 and 21 yield a fine crystalline powder from alcohol. All the substances are easily soluble in benzene and alcohol but are only slightly soluble in petroleum ether.

TABLE 2. Dichlorides of Urethan-N-Phosphoric Acids $ROCONHPOCl_2$

R	Yield (in %)	M. p.	Empirical formula	Equivalent found after hydrolysis*
$NC(CH_3)_2C$	70	90—92°	$C_5H_7O_3N_2PCl_2$	3.79, 3.73
$C_6H_5CH_2$	80	85—86	$C_8H_9O_3NPCl_2$	3.98, 3.96
$2\text{-}CH_3, 5\text{-}(CH_3)_2CHC_6H_3$	90	72—74	$C_{11}H_{14}O_3NPCl_2$	3.98, 3.97
$m\text{-}HOC_6H_4$	90	132—133	$C_7H_6O_4NPCl_2$	3.95, 3.90
$p\text{-}HOC_6H_4$	90	126—128	$C_7H_6O_4NPCl_2$	3.85, 3.96
$o\text{-}NO_2C_6H_4$	40	40—42	$C_7H_5O_5N_2PCl_2$**	3.91, 3.98
$p\text{-}NO_2C_6H_4$	38	88—90	$C_7H_5O_5N_2PCl_2$***	3.84, 3.86

* Calculated for all compounds: equiv. after hydrolysis: 4.00.

** Found %: N 9.10, 9.00. Calculated %: N 9.35.

*** Found %: N 9.21, 9.08. Calculated %: N 9.35.

It was pointed out previously [4] that the dichloride of isocyanatophosphoric acid "does not react at all with o- and p-nitrophenols." This has been found to be untrue; o- and p-nitrophenols do not react with the dichloride of isocyanophosphoric acid under the conditions (room temperature) that phenol does, but they do react with it on heating to 70-80° for a period of eight hours. Several dichlorides of urethan-N-phosphoric acids that have not been described in the literature were synthesized in this way (Table 2).

EXPERIMENTAL

The dichloride of isocyanatophosphoric acid. Phosphorus pentachloride (10 g moles) and 600 ml of dichloroethane were placed in a five-liter reaction vessel equipped with a stirrer, a heated dropping funnel, a reflux condenser and a thermometer (with the bulb in the reaction mixture). The oil bath on which it was placed was heated to 100-105°, and when the temperature of the reaction mixture reached 70-80°, 10 g moles of methyl- or ethylurethan, melted and heated to 70-80°, were poured in at a rate such that the temperature of the reaction mixture was maintained within the limits of 70-80°. This required about an hour at a bath temperature of 100-105°. The faster the urethan is added, the more the temperature of the reaction mixture falls. The temperature of the mixture should not be allowed to fall below 70°. The completion of the reaction can be determined by the disappearance of the last pieces of phosphorus pentachloride, by the cessation of gas formation, and by an increase in the temperature of the reaction mixture (while the temperature of the oil bath remains constant). The gases that are given off during the reaction are passed through a trap containing dichloroethane in order to absorb the dichloride of isocyanatophosphoric acid carried along by a current of hydrogen chloride and methyl or ethyl chloride. On completion of the reaction, the contents of the trap are combined with the reaction mixture and distilled in vacuo through a small column. The air which enters the capillary is dried over phosphorus pentoxide. The yield of the dichloride of isocyanatophosphoric acid is 90%; b.p. 55-58° at 20 mm.

It is possible to start with phosphorus trichloride. In this case a mixture of 10 g moles of phosphorus trichloride and a sufficient quantity of dichloroethane, carbon tetrachloride or chlorobenzene, while being stirred and cooled, is saturated with chlorine (the tube carrying the chlorine must be above the surface of the liquid). Then the mixture is heated to 70-80° and the process is carried on as described above. It is extremely convenient to use previously prepared isocyanophosphoryl dichloride as the solvent, which somewhat increases the yield.

Diesters of urethan-N-phosphoric acids (Table 1) and dichlorides of urethan-N-phosphoric acids (Table 2). To a solution of the dichloride of isocyanatophosphoric acid in petroleum ether, while cooled (0 - +5°) and stirred, is added an equivalent quantity of alcohol or phenol. The dichlorides of urethan-N-phosphoric acids precipitate in crystalline form. They are filtered off, washed with petroleum ether and dried in a vacuum over paraffin. For conversion to the diesters, the dichlorides are added to an excess of the corresponding alcohol, with stirring and cooling (+5, +10°). For one g mole of the dichloride, 600 ml of methyl, ethyl or isopropyl alcohol are used. After one hour the excess alcohol is distilled off in vacuo at 15-20°, and the residue is recrystallized. In order to prepare esters of phenol and high-boiling alcohols, the calculated quantity of phenol or alcohol is added (at 0°) to the reaction mixture in petroleum ether, and after one hour the petroleum ether is distilled off in vacuo.

Dichlorides of o- and p-nitrophenylurethan-N-phosphoric acids (Table 2). A mixture of 50 ml of benzene, 0.1 g mole of the dichloride of isocyanatophosphoric acid and 0.1 g mole of o- or p-nitrophenol is heated under a reflux condenser at 60-70° until the nitrophenol is completely dissolved, which requires ~8 hours, and the solution is allowed to stand at 15-20°. Within 12-15 hours the dichlorides of o- or p-nitrophenylurethan-N-phosphoric acids precipitate in crystalline form. They are filtered off, washed with petroleum ether and dried in vacuo over paraffin.

SUMMARY

The action of urethan on phosphorus pentachloride at 70-80° results in the formation of the dichloride of isocyanatophosphoric acid and the corresponding alkyl chlorides.

A number of dichlorides and diesters of alkyl- and arylurethan-N-phosphoric acids were prepared.

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ISOMERIC CONVERSION OF SULFONES OF THE NAPHTHALENE SERIES IN THE PRESENCE OF METAL HALIDES

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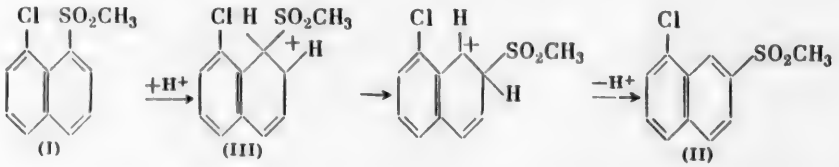
In a previous study [1] we ascertained that methyl-(1-chloro-naphthyl-8)-sulfone (I), on heating with concentrated hydrochloric acid at 200°, isomerizes to methyl (1-chloronaphthyl-7)-sulfone (II). Analogous results were obtained with ethyl-(1-chloronaphthyl-8)-sulfone. According to present ideas [2], isomeric conversion of aromatic compounds is caused by an attack on the molecule by a proton with the formation of a σ-complex (III) in which the change in position of the substituent takes place.*



(I) (III) (II)

In this case the addition of a proton to the carbon atom to which the substituent is attached, is facilitated as a result of the presence of steric hindrances to the transfer of atoms of chlorine and sulfur in the plane of the naphthalene nucleus (for further detail see [1]). In accordance with this, other isomeric methylchloronaphthylsulfones and unsubstituted methylnaphthylsulfones do not isomerize under the conditions indicated. It might, however, be assumed that isomeric conversion of sulfones, devoid of steric hindrances, are still possible under conditions in which there is a greater tendency of the medium to transfer a proton to a neutral base than in the case of an aqueous solution of hydrochloric acid.

This stimulated us to study the possibility of isomerizing aromatic sulfones by the action of hydrogen chloride in the presence of such catalysts as aluminum chloride, ferric chloride, etc. We first studied the behavior, under these conditions, of methyl-(1-chloronaphthyl-8)-sulfone, which is known to be capable of isomerization.

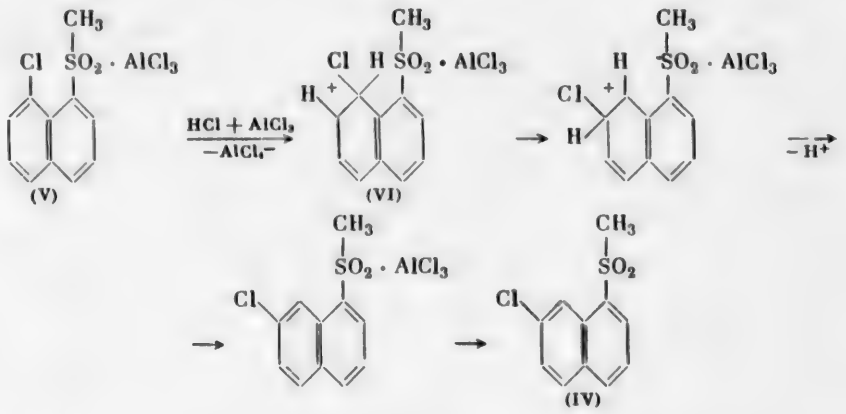
Preliminary experiments showed that it does not change on heating to 230-250° in a current of dry hydrogen chloride. However, on heating it for one hour at 125° in a current of hydrogen chloride with two moles of aluminum chloride, and after removing tarry material from the reaction product, a mixture was obtained in 52% yield which contained ~90% of methyl-(2-chloronaphthyl-8)-sulfone (IV) and ~4% of methyl-(1-chloronaphthyl-7)-sulfone (II) as determined from the infrared spectra. Thus, under these conditions, contrary to the expected principal direction of the reaction, migration of an atom of chlorine occurred, but there was no change of position of the methylsulphonyl group.

A change in the direction of isomerization of methyl-(1-chloronaphthyl-8)-sulfone may be explained by the fact that the sulfones form complexes with aluminum chloride in which the latter is linked to an oxygen of the sulfonyl group (see [3]).** The formation of a similar complex (V) increases the polarization of the bond between

* The addition of a proton and the transfer of the substituent to a neighboring carbon atom and the loss of a proton from it may, apparently, take place either successively or simultaneously, depending on the nature of the isomerized compound. Only in the first case may one speak of the intermediate formation of a σ-complex. At the present time, however, there are no data that would permit one to conclude which of these two mechanisms occurs in any specific case.

** Complexes of sulfones with antimony trichloride and pentachloride are also known [4].

sulfur and oxygen and likewise the positive charge on the sulfur atom. This, in turn, results in an increase in the partial positive charge on the carbon atom that is linked to the sulfur, thus making it more difficult for it to interact with a proton, and leading to the formation of a σ-complex (III). The formation of a complex of sulfone with



aluminum chloride has little influence, however, on the possibility of forming an isomeric σ-complex (VI) in the presence of more than one mole of aluminum chloride. Because of this a change in the case of migration of a methylsulfonyl group and an atom of chlorine also occurs.

The necessity of having more than one mole of aluminum chloride present in order for isomerization to occur, is confirmed by the fact that methyl-(1-chloronaphthyl-8)-sulfone remains practically unchanged on heating with 0.9 moles of aluminum chloride in a current of hydrogen chloride for three hours at 125°.

The concepts stated above permitted one to hope that aprotic acid such as ferric chloride and zinc chloride, which have a lesser tendency to form complexes than aluminum chloride, would prove to be more suitable catalysts for the isomerization of aromatic sulfones. As a matter of fact, on heating methyl-(1-chloronaphthyl-8)-sulfone with anhydrous ferric chloride (0.5 moles) in a current of hydrogen chloride for six hours at 150°, and after the removal of tarry substances, a mixture was obtained (yield 75%) containing ~92% of methyl-(1-chloronaphthyl-7)-sulfone (II) and ~2.5% of methyl-(2-chloronaphthyl-8)-sulfone (IV) as determined from the infrared spectra. Thus in this case, and also on heating with concentrated hydrochloric acid at 200°, the principal direction of the isomerization is the change in the position of the methylsulfonyl group.

Similar results were obtained on heating methyl-(1-chloronaphthyl-8)-sulfone with zinc chloride (0.5 moles) in a current of hydrogen chloride. When the reaction was carried on for six hours at 150°, a mixture (yield 68%), containing ~98% of methyl-(1-chloronaphthyl-7-sulfone and ~1% of methyl-(2-chloronaphthyl-8)-sulfone was obtained.

It should be noted that not in a single one of the cases described above was it possible to detect the original 1,8-isomer in the reaction products. Judging by the different infrared spectra of these products, their content of the 1,8-isomer cannot exceed 2.9% in the experiments with aluminum chloride, 1.5% in the case of ferric chloride, and 0.5% in the experiments with zinc chloride. The practically complete irreversibility of the isomerization of methyl-(1-chloronaphthyl-8)-sulfone is explained by the fact that, as a result of the repulsion of the peri-substituents it has a considerably greater free energy of formation than other isomers (compare the data on the energy of similar systems [5, 6]).

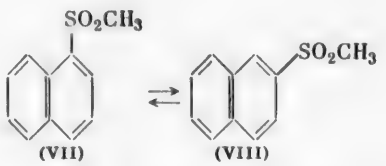
Moreover, in all cases of the isomerization of methyl-(1-chloronaphthyl-8)-sulfone, the change in position both of the methylsulfonyl group and the chlorine atom was only to the adjacent atom of the carbon ring. This indicates the intramolecular character of these isomerization processes. The same conclusion was drawn previously from a study of the isomerization of monochloro- and monomethylnaphthalenes in the vapor phase over aluminum silicate catalysts [7, 8].

In accordance with our original supposition, not only methyl-(1-chloronaphthyl-8)-sulfone, but also unsubstituted methyl-(naphthyl-1)-sulfone (VII) undergoes isomerization in the presence of ferric chloride and zinc

TABLE 1

Sample	Concentration (% by wt.)	Found: optical density at 605 cm⁻¹	Found: concentration of 2-isomer in soln. (% by wt.)	Found: concentration of 2-isomer in sample (in %)
Methyl-(naphthyl-2)-sulfone	0.386	0.180	—	—
	0.495	0.226		
	0.497	0.227		
	0.670	0.309		
Isomerization product of methyl-(naphthyl-1)-sulfone "d"	0.678	0.283	0.616	90.7
	0.692	0.290	0.634	91.8
	0.388	0.165	0.360	93.0
			Average	91.8
Isomerization product of methyl-(naphthyl-2)-sulfone "e"	0.692	0.306	0.668	96.7
	0.677	0.305	0.665	98.0
	0.367	0.162	0.353	96.3
			Average	97.0

chloride (in contrast to isomerization in the presence of hydrochloric acid). On heating it with 0.5 moles of zinc chloride in a current of hydrogen chloride for eight hours at 200°, a mixture was obtained (yield 85%) which was found to contain methyl-(naphthyl-2)-sulfone (VIII) and the original 1-isomer in a ratio of 96 : 4 from an analysis of the infrared spectra. A mixture of practically the same composition (97 : 3) was obtained by heating methyl-(naphthyl-2)-sulfone under the same conditions. Thus, in the case of the unsubstituted methylnaphthylsulfones, the isomerization process is reversible, while the equilibrium point is strongly displaced in the direction of the 2-isomer.



(VII) (VIII)

The isomerization of methyl-(naphthyl-1)-sulfone was also accomplished in the presence of ferric chloride (2 moles, 145°, 3 hours), but in this case a considerable formation of tar was observed, caused, apparently, by the oxidizing ability of this catalyst under these conditions (compare [9]). In the presence of aluminum chloride (2 moles) in a current of hydrogen chloride, however, methyl-(naphthyl-1)-sulfone (125°, 1 hour) did not noticeably isomerize. This was doubtless due to the same reason as the failure of the methylsulfonyl group to migrate, under analogous conditions, in the case of methyl-(1-chloronaphthyl-8)-sulfone. According to the literature [10], methyl-p-tolyl- and methyl-m-chlorophenylsulfones failed to isomerize when treated with aluminum chloride and hydrogen chloride (100°, 1.5 and 7 hours, respectively).

It is interesting to note that isomerization of methyl-(naphthyl-1)sulfone in the presence of zinc chloride and under the conditions given above, does not occur if hydrogen chloride is not passed into the reaction mixture. This once again confirms that isomerization of a similar series is connected with an attack on the molecule by a proton.

EXPERIMENTAL

(with the assistance of S. A. Kabanova)

Methyl-(naphthyl-1)-sulfone was prepared according to the literature [11] from 1-(naphthalenesulfinic acid, synthesized from 1-naphthylamine by the Gattermann method [12]. Its melting point was 101-102°; the literature [11] shows m.p. 102-103°. Methyl-(naphthyl-2)-sulfone was prepared from 2-naphthalenesulfochloride through 2-naphthalenesulfinic acid; m.p. 141-142°. The literature [11] shows 142-143°. Methylchloronaphthylsulfones. The synthesis of these compounds was described in a preceding paper [1].

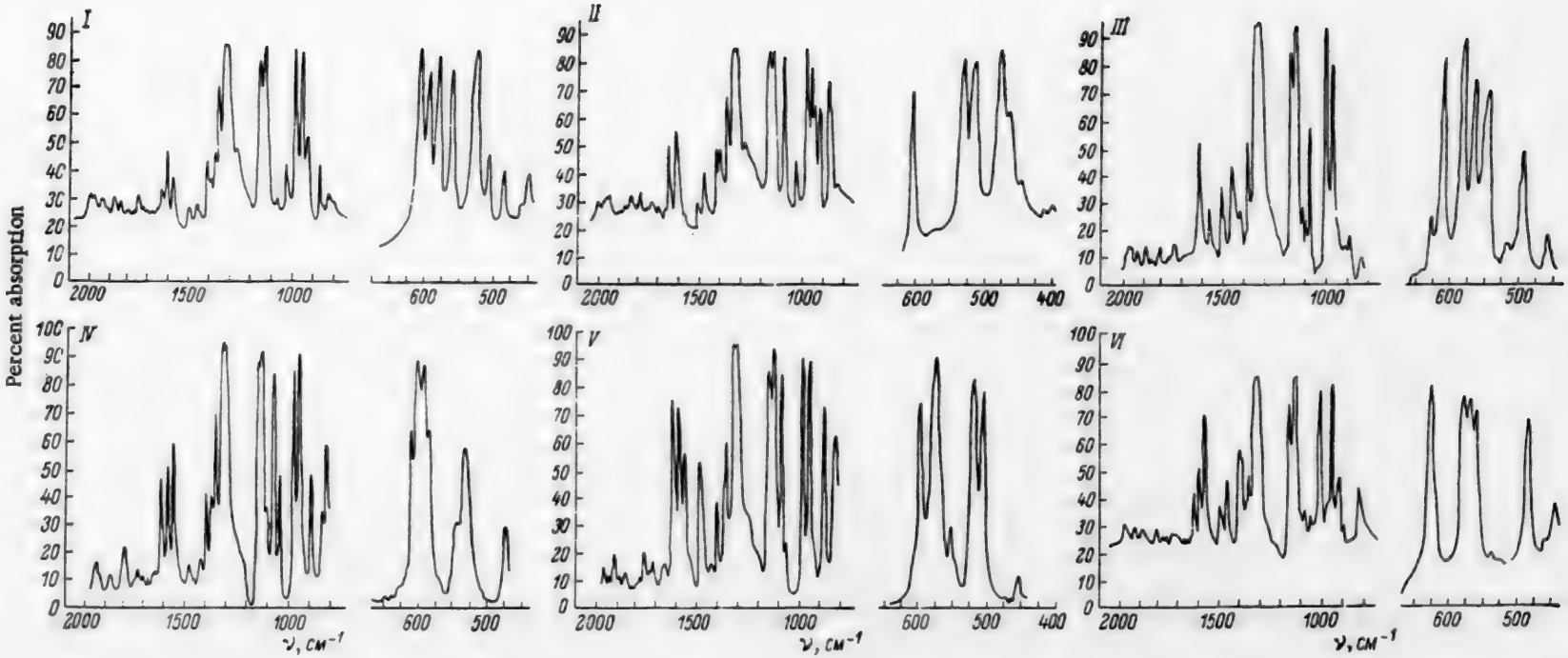


Fig. 1. Infrared spectra. I) Methyl-(naphthyl-1)-sulfone; II) methyl-(naphthyl-2)-sulfone; III) methyl-(1-chloronaphthyl-8)-sulfone; IV) methyl-(1-chloronaphthyl-7)-sulfone; V) methyl-(2-chloronaphthyl-8)-sulfone; VI) methyl-(chloronaphthyl-5)-sulfone.

TABLE 2

Sample	Concentration of solution (% by wt.)			Found		
	total	of the 1-isomer	of the 2-isomer	optical density at 560 cm^{-1}	concentration of 1-isomer in solution (% by wt.)	content of 1-isomer in sample (%)
Calibrated solutions		–	1.34	0.038	–	–
		0.0296	1.34	0.077		
		0.0862	1.34	0.151		
Isomerization product of methyl-(naphthyl-1)-sulfone "d"	1.41		1.30	0.110	0.055	3.9
Isomerization product of methyl-(naphthyl-2)-sulfone "e"	1.41		1.37	0.092	0.041	2.9

The Isomerization of Methyl-(1-Chloronaphthyl-8)-Sulfone

Experiment 1. 3.00 g of methyl-(1-chloronaphthyl-8)-sulfone (m.p. 124.5-126.0°) were heated, while being stirred, with 3.30 g of anhydrous aluminum chloride for one hour at a bath temperature of 125°. Dry hydrogen chloride was constantly passed into the reaction mixture at a rate of 30-40 ml/min. After cooling, the black mass was treated with 10% hydrochloric acid and carefully extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate, boiled thoroughly with carbon* and evaporated down. There remained 1.55 g of a brownish product "a" with m.p. 103-111°. After two recrystallizations from alcohol, a colorless crystalline substance, m.p. 117-118° was obtained. A mixed melting point test with the original sulfone melted at 82-90°, while a similar test with methyl-(2-chloronaphthyl-8)-sulfone (m.p. 117.5-118° [1]) showed no depression of the melting point. The ultraviolet spectrum** of the substance was also identical with that of methyl-(chloronaphthyl-8)-sulfone: λ_{max} 228.5 mμ (log ε 4.89), 285 mμ (log ε 3.7), 311.5 mμ (log ε 3.44) and 326 mμ (log ε 3.43).

The analyses of product "a" and of other reaction mixtures by means of infrared spectra are described below.

Experiment 2. 0.50 g of methyl-(1-chloronaphthyl-8)-sulfone were heated at 125° with 0.25 g of aluminum chloride for three hours. 0.49 g of a substance with a m.p. of 111-115° were separated from the reaction mixture; after recrystallization from alcohol, 0.35 g were obtained with a m.p. of 125-126°. A mixed melting point test with the original sulfone showed no depression.

Experiment 3. 1.00 g of methyl-(1-chloronaphthyl-8)-sulfone was heated with 0.34 g of anhydrous ferric chloride in a current of dry hydrogen chloride for six hours at a bath temperature of 150°. On working up the reaction mixture (as in Experiment 1), 0.75 g of a brown product "b" with a m.p. of 144-156° were obtained. After one recrystallization from alcohol, colorless crystals with m.p. 158.5-160.0° were obtained. A mixed melting point test with methyl-(chloronaphthyl-7)-sulfone (m.p. 160.5-161.0° [1]) showed no depression. Their ultraviolet spectra were also identical: λ_{max} 232 mμ (log ε 4.87), 285 mμ (log ε 3.72), 315 mμ (log ε 3.26) and 330 mμ (log ε 3.35).

Experiment 4. 1.00 g of methyl-(1-chloronaphthyl-8)-sulfone were heated with 0.28 g of anhydrous zinc chloride, with stirring, in a current of dry hydrogen chloride for six hours at a bath temperature of 150°. 0.68 g of a slightly colored product "c" with a m.p. of 137-156° were obtained from the reaction mixture in the usual way. On recrystallization from alcohol containing activated carbon, colorless crystals of methyl-(1-chloronaphthyl-7)-sulfone were obtained and identified, as in Experiment 3, by mixed melting point and ultraviolet spectra.

* It was found, through the study of the infrared spectra of artificial mixtures, that treatment with activated carbon does not change the ratio of sulfone isomers in the solution.

** The ultraviolet spectra of the methylchloronaphthylsulfones will be reported on separately. All spectra shown here were taken in alcohol solutions on an SF-4 spectrophotometer.

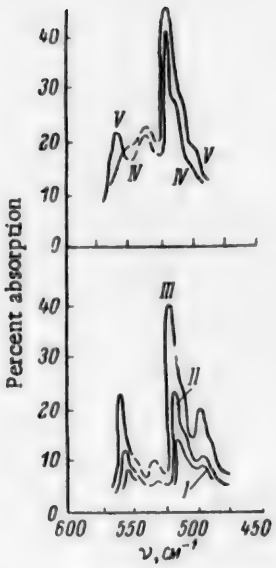


Fig. 2. Comparison of spectra of mixtures with a preponderant content of the 2,8-isomer. I-III) Calibrated solutions; IV) isomerization product "a"; V) the same with the addition of 2% 1,8 and 1,7-isomers.

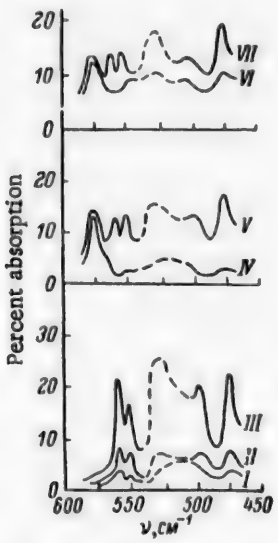


Fig. 3. Comparison of spectra of mixture with a preponderant content of the 1,7 isomer. I-III) Calibrated solutions; IV) isomerization product "c"; V) the same with the addition of 2% 1,8- and 2,8-isomers; VI) isomerization product "b"; VII) the same with the addition of 2% 1,8- and 2,8-isomers.

Experiment 5. 0.50 g of methyl-(1-chloronaphthyl-8)-sulfone were heated for 7.5 hours in a current of hydrogen chloride at 230-250°. On treating the reaction mass with water, 0.41 g of the slightly decomposed original product with a m.p. of 118-121° were obtained. After recrystallization from alcohol the m.p. was 125.5-126.5°; a mixed melting point test with the original sulfone showed no depression.

Isomerization of Methylnaphthylsulfones

Experiment 6. 1.00 g of methyl-(naphthyl-1)-sulfone and 1.58 g of anhydrous ferric chloride were heated, with stirring, for three hours in a current of hydrogen chloride (30-40 ml/min) at a bath temperature of 145°. After cooling, the dark tarry mass was treated with 10% of hydrochloric acid and extracted with ether. The ether solution was dried over calcium chloride and evaporated and the remaining sticky material was triturated with cold alcohol (twice per 1.5 ml). This yielded 0.28 g of a yellowish-brown product with a m.p. of 115-136.5°; after repeated recrystallization from alcohol, a colorless crystalline substance with m.p. 137.5-140.0° was obtained. A mixed melting point test with methyl-(naphthyl-2)-sulfone (m.p. 141-142°) showed no depression. Their ultraviolet spectra were also identical: λ_{max} 229 mμ (log ε 4.93), 277 mμ (log ε 3.65), 311 mμ (log ε 3.00) and 325 mμ (log ε 3.14).

Experiment 7. 2.00 g of methyl-(naphthyl-1)-sulfone were heated, with stirring, with 0.70 g of anhydrous zinc chloride for eight hours at a bath temperature of 200°, while dry hydrogen chloride was passed through simultaneously. The dark mass obtained was triturated with 10% of hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, boiled thoroughly with activated carbon, filtered, and the chloroform driven off. The remaining light yellowish product "d" melted at 126-139°; it weighed 1.70 g. On recrystallizing it from alcohol, methyl-(naphthyl-2)-sulfone with m.p. 140.5-141.5° was obtained; it was identified, as in the preceding experiment, by a mixed melting point and by its ultraviolet spectrum.

Experiment 8. 1.50 g of methyl-(naphthyl-2)-sulfone were heated with 0.50 g of anhydrous zinc chloride under the same conditions as in Experiment 7. 1.41 g of reaction product "e", m.p. 133-139° were separated as above. According to its infrared spectrum (see below) this product had a composition that was close to the composition of product "d" of the preceding experiment.

Experiment 9. This was carried out similarly to Experiment 7, but in the absence of hydrogen chloride. The original methyl-(naphthyl-1)-sulfone with m.p. 98-100° and a yield of 92% was separated from the reaction mixture.

Experiment 10. 0.50 g of methyl-(naphthyl-1)-sulfone and 0.65 g of aluminum chloride were heated, with stirring, in a current of dry hydrogen chloride for one hour at a bath temperature of 125°. 0.36 g of a brown product with m.p. 95-98.5° were separated in the usual way from the dark tarry mass; after recrystallization from alcohol the m.p. was 98-99.5°. A mixed melting point test with the original sulfone showed no depression.

TABLE 3

Concentration of the isomers of methylchloronaphthylsulfones (% by wt.)				Differential optical density in cm^{-1}			Refer to figure
in calibrated solutions			in a comparison solution of 2,8-isomer	558 (1,8-isomer)	499 (1,8-isomer)	520 (1,7-isomer)	
1,8-isomer	1,7-isomer	2,8-isomer					
0.040	0.037	3.00	3.00	0.038	0.036	0.075	2, *I*
0.082	0.080	3.00	3.00	0.058	0.050	0.129	2, *II*
0.170	0.152	3.00	3.00	0.129	0.108	0.269	2, *III*

TABLE 4

Mixture obtained by isomerizing methyl-(1-chloronaphthyl-8)-sulfone in the presence of	Found in the mixture (% by wt.)				
	1,8-isomer in bands		1,7-isomer in 520 cm^{-1} band	2,8-isomer in bands	
	558 cm^{-1}	499 cm^{-1}		551 cm^{-1}	476 cm^{-1}
Aluminum chloride	(2.9)	(2.9)	4.2		
Ferric chloride	(1.4)	(1.5)		2.6	2.3
Zinc chloride	(0.5)	(0.5)		1.1	0.8

Analysis of the Isomerization Products by Means of Infrared Absorption Spectra

The spectra of individual sulfones (Fig. 1, I-VI) and of the reaction mixtures were taken using 1.5% solutions in chloroform with a layer thickness of 1 mm on a double beam IKS-14 spectrophotometer.

Examination of the absorption spectra of reaction mixture "d" and "e", obtained from the isomerization of methyl-(naphthyl-1)- and methyl-(naphthyl-2)-sulfones, showed that these mixtures contain both isomers with a slight preponderance of methyl-(naphthyl-2)-sulfone. Quantitative determination of the content of the 2-isomer among the isomerization products was carried out by measuring the intensity of the absorption band of this compound at 605 cm^{-1} and comparing it with a previously constructed calibrated chart showing the dependence of the optical density [13] at 605 cm^{-1} on the concentration of the 2-isomer in solution.* Data relating to this analysis are shown in Table 1.

The absorption band at 560 cm^{-1} was used for analyzing mixtures for their content of methyl-(naphthyl-1)-sulfone. The absorption of the 2-isomer in this region is not great. However, inasmuch as the content of methyl-(naphthyl-2)-sulfone in the reaction mixtures exceeds the content of methyl-(naphthyl-1)-sulfone many times over, its contribution to the total absorption of the mixture at 560 cm^{-1} may be fairly large. In order to avoid corrections for the absorption of the 2-isomer, a definite quantity of methyl-(naphthyl-2)-sulfone was added to the solutions which were used for constructing the calibrated charts for the determination of methyl-(naphthyl-1)-sulfone. The solutions of the reaction mixtures were prepared for analysis in such a way that their content of the 2-isomer was the same as that of the calibrated solutions. Under these conditions, correction for the absorption of the 2-isomer is identical for all solutions, and takes place automatically. The analytical results are shown in Table 2.

We ran into considerable difficulty in analyzing the isomerization products of methyl-(1-chloronaphthyl-8)-sulfone. The spectrum of mixture "a", obtained during the isomerization of this sulfone in the presence of aluminum chloride, was practically identical with the spectrum of methyl-(2-chloronaphthyl-8)-sulfone. Similarly, the absorption spectra of isomerization products "b" and "c" (produced in the presence of ferric chloride and zinc chloride),

* The thickness of the layer in all analyses was 1 mm.

correspond with the spectrum of methyl-(1-chloronaphthyl-7)-sulfone. Inasmuch as it was determined with the artificial mixtures that it was impossible to detect small quantities (~3%) of isomeric methylchloronaphthyl-sulfones by the usual spectrophotomeric methods in the presence of a predominant quantity of one of them, we decided to use a more sensitive method of taking different absorption spectra [14] in order to determine the qualitative and quantitiative composition of products "a", "b" and "c". The essence of this method is to place in the comparison beam, instead of the pure solvent, a solution of the substance that is predominant in the sample to be analyzed. With equal concentrations of this substance in the working solution and in the comparison solution, the instrument records the absorption of the remaining components of the sample under analysis.

Determination of the content of the basic component among the isomerization products of methyl-(1-chloronaphthyl-8)-sulfone ("a", "b" and "c") was carried out similarly to the analysis of methyl-(naphthyl-2)-sulfone described above using absorption bands at 1080 cm^{-1} for methyl-(1-chloronaphthyl-7)-sulfone and at 1090 cm^{-1} for methyl-(2-chloronaphthyl-8)-sulfone. Analysis showed that product "a" contained 89.3 ± 0.7% of methyl-(2-chloronaphthyl-8)-sulfone and that products "b" and "c" contained 91.8 ± 1.3% and 97.9 ± 0.6% respectively of methyl-(1-chloronaphthyl-7)-sulfone.

The method of quantitative determination of mixtures with the aid of different spectra may be seen from the example of the analysis of reaction mixture "a". A series of calibrated solutions containing a constant quantity of the 2,8-isomer and varying quantities of the 1,8- and 1,7-isomers (see Table 3), a solution of the sample to be analyzed, and a solution of one 2,8-isomer (in the comparison beam) were used for the analysis. The concentration of the 2,8-isomer in all solutions was identical and amounted to 3.0% by weight.

Examination of the spectra of the calibrated solutions (Fig. 2, I-III) shows that absorption bands at 558 and 499 cm^{-1} for the 1,8-isomer and at 520 cm^{-1} for the 1,7-isomer clearly appear in them. In the 550-525 cm^{-1} region the absorption curves are shown as dotted lines, since within the interval practically complete absorption of radiation by the fundamental component and by the solvent occurs.

In the spectrum of the isomerization product of methyl-(1-chloronaphthyl-8)-sulfone in the presence of aluminum chloride (Fig. 2, IV) there is a distinct absorption band of the 1,7-isomer at 520 cm^{-1} from which its content in the reaction mixture was determined (see Table 4) by using a graduated scale based on the data of Table 3. The absorption bands at 558 and 499 cm^{-1}, corresponding to the 1,8-isomer, are absent. If we assume that they are masked by the absorption of other mixtures, the magnitudes of the optical densities at 558 and 499 cm^{-1} permit us to determine the upper limit of the possible content of the 1,8-isomer (corresponding magnitudes are shown in Table 4 in parentheses).

Determination of the content of methyl-(1-chloronaphthyl-8)-sulfone and methyl-(2-chloronaphthyl-8)-sulfone in products "b" and "c", obtained by carrying out the isomerization in the presence of ferric chloride and zinc chloride, was accomplished in similar fashion. The corresponding spectra are shown in figure 3. The 2,8-isomer was determined from the 551 and 476 cm^{-1} bands. The results of the analysis are shown in Table 4.

In the spectra of products "b" and "c" there is an absorption band at 575 cm^{-1}. It is possible that the appearance of this band is due to the presence in these products of small quantities of methyl-(1-chloronaphthyl-5)-sulfone, which has an intense absorption band at 578 cm^{-1}.

SUMMARY

1. By using the methylnaphthylsulfones as examples, the possibility of the catalytic isomerization of sulfones as a result of the migration of an alkylsulfonyl group from one position in the aromatic ring to another, was demonstrated for the first time. It was shown, in particular, that methyl-(naphthyl-1)-sulfone, on being heated with zinc chloride or ferric chloride at 200° in a current of hydrogen chloride, is converted into the 2-isomer. The isomerization is reversible, and on achieving equilibrium, the mixture contains 3-4% of methyl-(naphthyl-1)-sulfone and 96-97% of the 2-isomer.

2. Methyl-(1-chloronaphthyl-8)-sulfone, depending on the nature of the catalyst, isomerizes either to methyl-(1-chloronaphthyl-7)-sulfone owing to the change in position of the methylsulfonyl group (with ferric chloride or zinc chloride), or to methyl-(2-chloronaphthyl-8)-sulfone owing to the migration of a chlorine atom (with aluminum chloride). In both cases the isomerization process is practically irreversible.

3. A method for the quantitative analysis of mixtures of isomeric sulfones of the naphthalene series using infrared spectra was worked out.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

STUDIES OF THE 1,5-DIARYL-3-HALO-FORMAZAN SERIES

II. THE SYNTHESIS OF ARYLAZOCHLOROACETIC ACIDS

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In the preceding paper [1] we described the synthesis of halo- and dihalo-substituted 1,5-diaryl-3-chloroformazans. By-products of this synthesis are the arylazochloroacetic acids (I) which have been little studied. On

$$RNH_2 \longrightarrow [R{-}N{\equiv}N]^+Cl^- \xrightarrow{CHCl(COOK)_2} \longrightarrow R{-}N{=}N{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}COOH \longrightarrow R{-}NH{-}N{=}\underset{\displaystyle Cl}{\underset{|}{C}}{-}COOH,$$

(I)

reacting with a second molecule of a diazo compound, they form substituted 1,5-diaryl-3-chloroformazans (II):

$$\begin{matrix} R{-}N{=}N \\ R{-}NH{-}N \end{matrix}\!\!>\!C{-}Cl$$

(II)

Only the o-carbomethoxy-, o-chloro- and 2,4-dimethylphenylazochloroacetic acids are known in the literature [2]. The arylazochloroacetic acids are of interest as starting products for the synthesis of unsymmetrical formazans (II). In addition, since they possess a mobile halogen atom, they must enter into exchange reactions with nucleophilic agents. According to the opinion of Fusco and Romani [2], the arylazochloroacetic acids are unstable compounds. When substituents are located in the ortho-position relative to the hydrazo group their stability is greatly increased, and only then is it possible to prepare and identify individual compounds. In our previous paper we showed that Fusco and Romani's statement that only the ortho-substituted arylazochloroacetic acids are stable, is incorrect. We found the conditions which permitted us to prepare the then unknown phenylazochloroacetic acid, and also various ortho-, meta-, para-, mono- and di-substituted arylazochloroacetic acids with satisfactory yields. It should be noted that the yields of arylazochloroacetic acids with electron-accepting substituents in the ring are higher than in compounds containing substituents that are electron donors (see the Table).

The arylazochloroacetic acids are crystalline and often occur as platelets or needles; they decompose on melting. They are pale yellow (I-XIV, XVI- XXIII); yellow-orange (XV, XXIV, XXV, XXVII, XXVIII, XXX-XXXIII); red-orange (XXVI, XXIX, XXXV) or brown (XXXIV). They dissolve easily in dioxane, pyridine, acetone, methyl and ethyl alcohol and in ether. They are less soluble in dichloroethane, chloroform, carbon tetrachloride, glacial acetic acid and petroleum ether; they are insoluble in water. Products (I-VII) were recrystallized from dichloroethane; products (VIII-XXIII) from a 10 : 1 mixture of dichloroethane and dioxane; products (XXIV-XXXV) from dioxane.

The figure shows the absorption spectra of some derivatives of phenylazochloroacetic acid in alcohol. The measurements were carried out on an SF-4 spectrophotometer. It is characteristic of phenylazochloroacetic acid and its substituted derivatives to show three peaks on the ultraviolet absorption curves in the following regions: 230-240 mμ, 280-305 mμ and 320-365 mμ. The peaks of substituted phenylazochloroacetic acids are displaced toward the longer wave region. α-Naphazochloroacetic acid has two peaks on the absorption curve at 224 and 240 mμ and one at 337 mμ.

Arylazochloroacetic Acid

$$R-NH-N=\underset{\displaystyle Cl}{\overset{\displaystyle |}{C}}-COOH$$

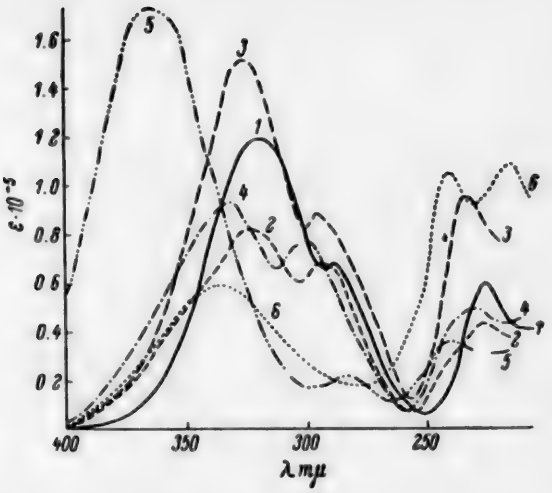
Compound	R	Yield %	M.p.	Empirical formula	% N found	% N calculated
I	C_6H_5	31	129°	$C_8H_7O_2N_2Cl$	14.05, 14.02	14.10
II	o-$CH_3C_6H_4$	21	161	$C_9H_9O_2N_2Cl$	13.05, 12.95	13.17
III	m-$CH_3C_6H_4$	19	156	$C_9H_9O_2N_2Cl$	13.09, 12.88	13.17
IV	p-$CH_3C_6H_4$	23	153	$C_9H_9O_2N_2Cl$	13.35, 13.21	13.17
V	o-$CH_3OC_6H_4$	25	172	$C_9H_9O_3N_2Cl$	12.23, 12.13	12.25
VI	p-$CH_3OC_6H_4$	4	161	$C_9H_9O_3N_2Cl$	12.54, 12.41	12.25
VII	2,5-$(C_2H_5O)_2C_6H_3$	23	157	$C_{12}H_{15}O_4N_2Cl$	9.60, 9.48	9.77
VIII	m-FC_6H_4	62	162	$C_8H_6O_2N_2FCl$	13.22, 13.11	12.93
IX	p-FC_6H_4	31	175	$C_8H_6O_2N_2FCl$	13.13, 13.07	12.93
X	m-ClC_6H_4	75	180	$C_8H_6O_2N_2Cl_2$	11.95, 11.76	12.02
XI	p-ClC_6H_4	62	183	$C_8H_6O_2N_2Cl_2$	12.03, 11.91	12.02
XII	o-BrC_6H_4	33	182	$C_8H_6O_2N_2ClBr$	10.36, 10.32	10.09
XIII	p-BrC_6H_4	61	185	$C_8H_6O_2N_2ClBr$	10.35, 10.14	10.09
XIV	o-IC_6H_4	40	178	$C_8H_6O_2N_2Cl$	8.85, 8.73	8.63
XV	p-IC_6H_4	58	171	$C_8H_6O_2N_2Cl$	8.80, 8.66	8.63
XVI	2,3-$Cl_2C_6H_3$	42	183	$C_8H_5O_2N_2Cl_3$	10.22, 10.13	10.47
XVII	2,4-$Cl_2C_6H_3$	42	181	$C_8H_5O_2N_2Cl_3$	10.51, 10.36	10.47
XVIII	2,5-$Cl_2C_6H_3$	43	191.5	$C_8H_5O_2N_2Cl_3$	10.52, 10.51	10.47
XIX	3,4-$Cl_2C_6H_3$	70	167	$C_8H_5O_2N_2Cl_3$	10.44, 10.33	10.47
XX	2,4-$Br_2C_6H_3$	43	156	$C_8H_5O_2N_2ClBr_2$	7.94, 7.84	7.86
XXI	2,5-$Br_2C_6H_3$	44	198	$C_8H_5O_2N_2ClBr_2$	7.78, 7.72	7.86
XXII	3,5-$Br_2C_6H_3$	36	194	$C_8H_5O_2N_2ClBr_2$	7.69, 7.64	7.86
XXIII	2,5-$Cl_2CF_3C_6H_3$	32	190	$C_9H_5O_2N_2F_3Cl_2$	9.32, 9.12	9.30
XXIV	p-$NCSC_6H_4$	39	180—182	$C_9H_6O_2N_3SCl$	16.07, 15.98	16.43
XXV	m-$CH_3COC_6H_4$	58	202.5	$C_{10}H_9O_3N_2Cl$	11.51, 11.42	11.64
XXVI	p-$CH_3COC_6H_4$	59	176	$C_{10}H_9O_3N_2Cl$	11.72, 11.61	11.64
XXVII	o-$O_2NC_6H_4$	61	212	$C_8H_6O_4N_3Cl$	17.31, 17.12	17.25
XXVIII	m-$O_2NC_6H_4$	50	204	$C_8H_6O_4N_3Cl$	17.25, 17.15	17.25
XXIX	p-$O_2NC_6H_4$	42	197	$C_8H_6O_4N_3Cl$	17.40, 17.33	17.25
XXX	2,4-$O_2N, CH_3C_6H_3$	56	190	$C_9H_8O_4N_3Cl$	16.16, 15.98	16.31
XXXI	2,5-$OCH_3, O_2NC_6H_3$	42	197	$C_9H_8O_5N_3Cl$	15.51, 15.47	15.30
XXXII	2,5-Br, $O_2NC_6H_3$	62	197	$C_8H_5O_4N_3ClBr$	13.02, 12.86	13.03
XXXIII	p-$C_2H_5OOCC_6H_4$	28	194	$C_{11}H_{11}O_4N_2Cl$	10.27, 10.24	10.35
XXXIV	-α-$C_{10}H_7$	31	171	$C_{12}H_9O_2N_2Cl$	11.52, 11.39	11.26
XXXV	2-Br-β-$C_{10}H_6$	25	196	$C_{12}H_8O_2N_2ClBr$	8.68, 8.54	8.55

EXPERIMENTAL

m-Aminoacetophenone was prepared by the nitration of acetophenone [3] and the reduction of m-nitroacetophenone by iron in the presence of acetic acid [4]. p-Thiocyanoaniline was synthesized by the thiocyanation of aniline [5]. 2-Bromo-5-nitroaniline was prepared by the bromination of m-nitroaniline with bromine in acetic acid [6].

All the compounds shows in the table were prepared in an analogous manner from m-nitrophenylazoacetic acid.

m-Nitrophenylazoacetic acid (XXVIII). 6.7 g of m-nitroaniline were dissolved in 26 ml of 16% hydrochloric acid and diazotized at 0-5° by a solution of 3.8 g of sodium nitrite in 10 ml of water. The diazo solution was filtered and, with good stirring and cooling to 0°, 16 g of the dipotassium salt of chloromalonic acid and 22 g of sodium acetate in 200 ml of water were rapidly added. After a ten minute wait, the yellow-orange solution was filtered into a 45-50% sulphuric acid solution (180-190 ml) cooled to 0°. The precipitate – a mixture of the potassium salt of arylazochloroacetic acid and 1,5-di-(m-nitrophenyl)-3-chloroformazan – was washed several times on the filter with warm water, and the wash water added to the filtrate. The solution was allowed to stand at room temperature for two to three days and then the fine crystalline yellow precipitate was filtered off, washed on the filter



Absorption spectra of solutions of arylazochloroacetic acids. 1) Phenylazochloroacetic acid; 2) p-fluorophenylazochloroacetic acid; 3) p-methylphenylazochloroacetic acid; 4) p-methoxyphenylazochloroacetic acid; 5) p-nitrophenylazochloroacetic acid; 6) α-naphthylazochloroacetic acid. For curves 1-3 and 5) c is $3.75 \cdot 10^{-5}$ M; for curve 4) c is $7.6 \cdot 10^{-5}$ M; for curve 6) c is $1.0 \cdot 10^{-5}$ M.

with cold water until it showed a neutral reaction, and then dried in vacuo. The yield was 6 g (50%, calculated on the original amine). The product was recrystallized from dioxane. In order to get better yields in the synthesis of unsubstituted and alkyl- and alkoxy-substituted arylazochloroacetic acids, the mixture, after the addition of the diazo solutions, is stirred for a longer time.

SUMMARY

1. Conditions for the synthesis of various ortho-, meta-, para-, mono- and di-substituted arylazochloroacetic acids were found.

2. Thirty-five new substituted arylazochloroacetic acids were described.

3. The ultraviolet absorption spectra of some of the compounds prepared were determined.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESIS OF CERTAIN 1,2- AND 1,5-GLYCOL ETHERS

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In order to synthesize new plasticizers and high-boiling solvents a number of bifunctional compounds [1, 2] of the general structure given below were hydrogenated in the presence of platinum at ordinary pressure and Raney nickel at 25-30 atm.

$$C_2H_5OCH_2CH_2C(R)=CHCH_2X \quad \text{and} \quad (C_2H_5OCH_2CH_2C(R)=CHCH_2)_2O$$

R = H, CH_3 and Cl; X = OH, AlkO and $HN(CH_3)_2$.

It was found that instead of the scarce butyl alcohol, 1,3-dichlorobutene-2, an industrial waste product, may be used for the synthesis of high-boiling and expensive solvents. Especially valuable are: dibutyl ether (I), butylcellosolve (II), dibutylcellosolve (III), and butylcarbitol.

$$(CH_3CCl=CHCH_2)_2O \xrightarrow{H_2} \underset{(I)}{C_4H_9OC_4H_9} \qquad \underset{(II)}{C_4H_9OCH_2CH_2OH}$$

$$\uparrow \qquad\qquad H_2 \uparrow (R=H)$$

$$CH_3CCl=CHCH_2Cl + HOCH_2CH_2OR \xrightarrow{NaOH} CH_3CCl=CHCH_2OCH_2CH_2OR$$

$$CH_3CCl=CHCH_2Cl \downarrow (R=H)$$

$$\underset{(III)}{C_4H_9O(CH_2)_2OC_4H_9} \xleftarrow{H_2} \underset{R=H,\ CH_2CH_2OH.}{CH_3CCl=CHCH_2O(CH_2)_2OCH_2CH=CClCH_3}$$

For the hydrogenation of compounds with the chlorovinyl group an autoclave was charged with the corresponding unsaturated compound, an equimolar quantity of powdered potassium hydroxide or sodium hydroxide, and a small amount of Raney nickel activated by Adams platinum catalyst.

In order to identify the compounds obtained they were also synthesized from the corresponding compounds by splitting-out hydrogen chloride by means of alcoholic alkali, followed by hydrogenation.

$$\left.\begin{array}{l} CH_3OCH_2CH_2CCl=CHCH_2X \\ \qquad\downarrow -HCl \\ CH_3OCH_2CH_2C\equiv CCH_2X \end{array}\right\} \xrightarrow{H_2} CH_3OCH_2CH_2CH_2CH_2CH_2X$$

X = $N(CH_3)_2$, OCH_3.

Bis(5-ethoxypentyl) ether was prepared by hydrogenation both of bis(5-ethoxypenten-2-yl) ether and bis(3-chloro-5-ethoxypenten-2-yl) ether under hydrogen pressure.

$$\left.\begin{array}{l} (C_2H_5OCH_2CH_2CCl=CHCH_2)_2O \\ (C_2H_5OCH_2CH_2CH=CHCH_2)_2O \end{array}\right\} \xrightarrow{H_2} (C_2H_5OCH_2CH_2CH_2CH_2CH_2)_2O$$

TABLE 1

Structural formula	Yield %	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Found (%) Cl	N	C	H	Calculated (%) Cl	N	C	H
$CH_3CCl{=}CHCH_2OCH_2CH_2OH$	81.5	95—96° (2.5)	1.4710	1.1143	37.54	37.47	23.65, 23.30	—	—	—	23.58	—	—	—
$CH_3CCl{=}CHCH_2OCH_2CH_2OCH_2CH{=}CClCH_3$	78	107—108 (2)	1.4820	1.1029	61.75	60.47	29.62	—	—	—	29.71	—	—	—
$CH_3CCl{=}CHCH_2OCH_2CH_2OCH_2CH_2OH$	74	116—117 (1)	1.4720	1.1182	48.69	48.35	18.31	—	—	—	18.25	—	—	—
$C_2H_4OCH_2CH_2C(CH_3){=}CHCH_2OC_2H_5$ [1]	66.1	84—85 (10)	1.4390	0.8884	50.92	51.20	18.41 —	—	69.40, 69.51	11.50, 11.20	—	—	69.76	11.62
$C_2H_4OCH_2CH_2C(CH_3){=}CHCH_2OC_4H_{11}$-iso	59.5	124—127 (15)	1.4391	0.8539	65.90	65.05	—	—	72.98	12.39	—	—	72.80	12.00
$C_2H_4OCH_2CH_2C(CH_3){=}CHCH_2OH$	85.3	93—95 (14)	1.4528	0.9376	41.49	41.85	—	—	65.95, 65.25	10.62, 10.49	—	—	66.60	11.10
$C_2H_4OCH_2CH_2C(CH_3){=}CHCH_2OCOCH_3$	61.1	82—84 (2)	1.4462	0.9675	51.07	51.21	—	—	64.54, 64.66	9.84, 9.76	—	—	64.52	9.67
$C_2H_4OCH_2CH_2C(CH_3){=}CHCH_2N(CH_3)_2$	57.6	87—88 (16)	1.4435	0.8337	54.33	53.49	—	8.51, 8.58	—	—	—	8.18	—	—
$C_2H_4OCH_2CH_2CH{=}CHCH_2OC_2H_5$	76.5	79—81 (14)	1.4322	0.8877	46.09	46.58	—	—	68.51, 67.99	11.41, 11.42	—	—	68.35	11.39
$C_2H_4OCH_2CH_2CH{=}CHCH_2OC_4H_{11}$-iso	45	111—113 (12)	1.4350	0.8543	60.88	60.44	—	—	71.84, 71.92	11.98, 12.21	—	—	72.00	12.00
$C_2H_4OCH_2CH_2CH{=}CHCH_2OH$	76.8	92—94 (12)	1.4470	0.9238	37.56	37.22	—	—	64.30, 64.12	11.39, 11.28	—	—	64.61	10.77
$C_2H_4OCH_2CH_2CH{=}CHCH_2OCOCH_3$	71.9	94—95 (14)	1.4382	0.9686	46.50	46.59	—	—	62.75, 62.97	10.20, 9.79	—	—	62.70	9.30
$C_2H_4OCH_2CH_2CH{=}CHCH_2N(CH_3)_2$	77.7	71—72 (11)	1.4350	0.8218	49.80	48.88	—	9.10, 9.26	—	—	—	8.92	—	—
$C_2H_4OCH_2CH_2CH{=}$ HC C_4H	52	106—108 (2)	1.5069	0.9471	59.50	59.80	—	—	82.62, 82.37	9.43, 9.44	—	—	82.10	9.47
$(C_2H_4OCH_2CH_2CH{=}CHCH_2)_2O$	62.2	134—136 (2.5)	1.4545	0.9154	71.64	70.86	—	—	69.02, 69.28	10.83, 10.76	—	—	69.42	10.74
$(C_2H_4OCH_2CH_2CCl{=}CHCH_3)_2O$	42	156—159 (2)	1.4802	1.0830	81.51	80.59	22.61	—	—	—	22.80	—	—	—

TABLE 2

Structural formula	Yield %	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Found (%)			Calculated (%)		
								H	N	C	H	N
$C_2H_5O(CH_2)_2CH(CH_2)_2OC_2H_5$ CH_3	91.5	86—87° (27)	1.4111	0.8345	51.71	51.67	68.67, 69.01	12.52, 12.58	—	68.96	12.64	—
$C_2H_5O(CH_2)_2CH(CH_2)_2OC_5H_{11}$=iso CH_3	83.6	88—90 (12)	1.4001	0.8071	64.71	65.50	72.43	12.61	—	72.20	12.90	—
$C_2H_5O(CH_2)_2CH(CH_2)_2OH$ CH_3	84.5	86—88 (27)	1.4340	0.9059	41.91	42.41	65.94, 65.81	12.18, 12.30	—	65.75	12.32	—
$C_2H_5O(CH_2)_2CH(CH_2)_2OCOCH_3$ CH_3	92.5	101—103 (15)	1.4305	0.9408	50.97	51.67	63.68, 63.40	10.45, 10.33	—	63.80	10.63	—
$C_2H_5O(CH_2)_2CH(CH_2)_2N(CH_3)_2$ CH_3	91.5	110—112 (75)	1.4280	0.8222	54.07	53.96	—	—	8.31, 8.22	—	—	8.09
$C_2H_5O(CH_2)_5OC_2H_5$	85	68—70 (16)	1.4086	0.8371	47.21	47.05	67.18	12.59	—	67.50	12.50	—
$C_2H_5O(CH_2)_5OC_5H_{11}$=iso	90	106—108 (14)	1.4109	0.8276	61.00	60.90	71.41, 71.47	13.01, 13.10	—	71.28	12.87	—
$C_2H_5O(CH_2)_5OH$	90	80—82 (16)	1.4272	0.8993	37.55	37.69	64.13, 64.20	11.93, 11.67	—	63.64	12.12	—
$CH_3O(CH_2)_5OH$	92	150—153 (110)	1.4235	0.8718	33.41	33.08	61.99, 61.94	12.11, 12.10	—	61.02	11.86	—
$CH_3O(CH_2)_5N(CH_3)_2$[5] *	89.2	86—88 (33)	1.4350	*								
$C_2H_5O(CH_2)_5N(CH_3)_2$	96.6	70—72 (16)	1.4260	0.8125	50.07	49.34	—	—	8.74, 8.69	—	—	8.80
$C_2H_5O(CH_2)_5$	96.5	102—103 (4)	1.4867	0.9233	59.68	60.27	81.31	10.41	—	81.25	10.42	—
$[C_2H_5O(CH_2)_5]_2O$	98	120—121 (3)	1.4310	0.8810	71.98	71.78	69.19, 68.90	11.99, 12.27	—	68.29	12.19	—
$C_4H_9OC_4H_9$[6]	88.2	135—138 (680)	1.4019	0.7721								
$C_4H_9O(CH_2)_2OH$[6]	89.1	166—170 (680)	1.4265	0.9001								
$C_4H_9O(CH_2)_2O(CH_2)_2OH$[6]	91.2	222—226 (680)	1.4341	0.9665								
$C_4H_9O(CH_2)_2OC_4H_9$	92.5	188—192 (680)	1.4170	0.8496	51.40	51.66	68.81	12.81	—	68.96	12.64	—

* Picrate m.p. 78°.

EXPERIMENTAL

Bis(γ-chlorocrotyl) ether. This was synthesized by a known method [3]; b.p. 92-94° at 4 mm, n_D^{20} 1.4812, d_4^{20} 1.1033, which correspond to literature data.

γ-Chlorocrotylcellosolve. To a mixture of 0.5 mole of potassium hydroxide and 0.5 mole of ethylene glycol, 0.5 mole of 1,3-dichlorobutene-2 was added during 30 min with continuous stirring. The reaction mass was then heated in a boiling water bath for 6 hr. The reaction product was extracted with ether, washed with water, dried with magnesium sulfate, the ether driven off, and the residue distilled in vacuo.

The rest of the ethers were synthesized by the method described above (Table 1).

3-Methyl-5-ethoxypenten-2-ol-1. A mixture of 20 g of 1-chloro-3-methyl-5-ethoxypentene-2 and 150 ml of 20% potassium carbonate solution was boiled in a water bath for 8 hr. The reaction mass was extracted with ether, dried with magnesium sulfate, the ether driven off, and the residue distilled in vacuo (Table 1).

Addition of chloromethyl ethyl ether to divinyl. A 160 g quantity of divinyl, 260 g of chloromethyl ethyl ether, and 3 g of freshly-fused zinc chloride [1] in 200 ml of dry ether gave 298 g of a mixture of chlorides.

Fraction 1 was 3-chloro-5-ethoxypentene-1 (yield 63.7%): b.p. 62-64° (21 mm), n_D^{20} 1.4362, d^{20} 0.9561, MR_D 40.32; calc. 40.57.

Found %: Cl 24.11, 23.69. $C_7H_{13}OCl$. Calculated %: Cl 23.90.

Fraction 2 was 1-chloro-5-ethoxypentene-2 (yield 36.3%): b.p. 78-81° (20 mm), n_D^{20} 1.4508, d_4^{20} 0.9929, MR_D 40.07; calc. 40.57.

Found %: Cl 23.81, 23.75. $C_7H_{13}OCl$. Calculated %: Cl 23.90.

Hydrogenation of chlorovinyl-containing unsaturated compounds (Table 2). A mixture of equimolar quantities of the chlorovinyl-containing compound (diluted 2- to 3-fold in anhydrous alcohol) and sodium hydroxide or potassium hydroxide was hydrogenated under 25-30 atm hydrogen pressure in the presence of Raney nickel activated by addition of platinum catalyst (after Adams).

1-Dimethylamino-5-methoxypentene [5] was prepared by hydrogenating 3-chloro-1-dimethylamino-5-methoxypentene-2 by the above-described method and by hydrogenating 1-dimethylamino-5-methoxypentene-2 [1] in the presence of platinum catalyst.

Bis(5-ethoxypentyl) ether was prepared by hydrogenating bis(5-ethoxypenten-2-yl) ether and bis(3-chloro-5-ethoxypenten-2-yl) ether by the method described above.

SUMMARY

1. It was shown that it is feasible to use an industrial waste product—1,3-dichlorobutene-2—for the synthesis of dibutyl ether, butyl cellosolve, dibutylcellosolve, butylcarbitol, and butyl ethers in general.

2. It was found that unsaturated chlorovinyl compounds containing chlorine at the double bond are hydrogenated under 25-30 atm hydrogen pressure in the presence of Raney nickel.

3. A number of new unsaturated bifunctional compounds were synthesized and their hydrogenated derivatives prepared for the purpose of synthesizing new and previously-known high-boiling solvents.

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SUBSTITUTION OF OXYGEN BY SULFUR IN ORGANOPHOSPHORUS COMPOUNDS

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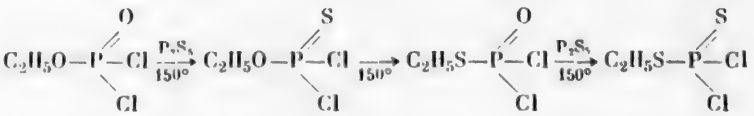
A convenient method for synthesizing alkyl- and dialkylthiophosphinyl chlorides was found earlier [1], and it was shown that when phosphinyl chlorides are heated with phosphorus pentasulfide to 135-160° for 4-6 hr, oxygen is replaced with sulfur.

It was of interest to investigate the possibility of applying this reaction to other types of organophosphorus compounds, such as alkyl- and arylphosphoryl chlorides, triaryl phosphates, and phosphoric and alkanephosphonic acid amides and amidochlorides. It was found that on treatment of ethyl dichlorophosphate with phosphorus pentasulfide under ordinary conditions, oxygen is replaced with sulfur; this results in a mixture of products, consisting of O-ethyl dichlorothiophosphate, S-ethyl dichlorothiophosphate, and ethyl dichlorodithiophosphate, the formation of which may be explained by the ability of O-ethyl dichlorothiophosphate to isomerize under the reaction conditions:



The possibility of isomerization of this type was confirmed by the fact that heating of ethyl dichlorophosphate, as well as O-ethyl dichlorothiophosphate, with an excess of phosphorus pentasulfide leads mainly to S-ethyl dichlorodithiophosphate. On the other hand, treatment with phosphorus pentasulfide of arylphosphoryl chlorides and triaryl phosphates, the thiono analogs of which can undergo thermal isomerization only to a very slight degree, leads to smooth replacement of oxygen with sulfur, the corresponding arylthionophosphoryl chlorides and triaryl thionophosphates being formed in yields from 45 to 66% (Table 1).

On treatment of phosphoric and methanephosphonic acid amidochlorides with phosphorus pentasulfide, replacement of oxygen with sulfur also takes place. In order to carry out this reaction, however, prolonged heating (10-12 hr) is necessary; the yield of the corresponding thiono derivatives decreases with increase in the number of dialkylamido groups and the size of the hydrocarbon radical in the dialkylamido group (Table 2). Complete amides, such as phosphoric acid hexamethyl- and hexaethyltriamides or methanephosphonic acid tetramethyl- and tetraethyldiamides do not react with phosphorus pentasulfide to replace oxygen with sulfur under ordinary conditions.

EXPERIMENTAL

1. Ethyl dichlorodithiophosphate. A mixture of 32 g (0.2 mole) of ethyl dichlorophosphate and 22 g (0.1 mole) of P_2S_5 was heated in a current of nitrogen to 150° for 5 hr, after which all the liquid part was distilled from the reaction mass in vacuo, washed with water, and dried in ethereal solution over anhydrous sodium sulfate. After removing the ether the residue was distilled in vacuo. Yield 8.5 g (23%).

B.p. 61-62° at 3 mm, d_4^{20} 1.4246, n_D^{20} 1.5904, MR_D 46.17; calc. 45.49. *

Literature data [8]: b.p. 92° (10 mm), d_0^0 1.445.3.

Found %: C 12.4, 12.5; H 2.8, 2.9; P 15.8, 15.9. $C_2H_5PS_2Cl_2$. Calculated %: C 12.3; H 2.6; P 15.9.

* The group refraction of two sulfur atoms was taken to be 18.72 [9].

TABLE 1

Formula	Boiling point (pressure in mm) or melting point	Melting point according to literature	Yield (in %)
$C_6H_5OP(S)Cl_2$	107—107.5° (3)	—	45
$p\text{-}CH_3C_6H_4OP(S)Cl_2$	91—92 (3)	—	53
$(C_6H_5O)_2P(S)Cl$	66—67	66—67° [2]	45
$(p\text{-}CH_3C_6H_4O)_2P(S)Cl$	51—52	53 [3]	45
$(C_6H_5O)_3P(S)$	49—50	49—50 [4]	66
$(p\text{-}CH_3C_6H_4O)_3P(S)$	87—88	87 [5]	64

TABLE 2

Formula	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Yield (in %)
$(CH_3)_2NP(S)Cl_2$*	75—76°(10)	1.5404	1.3767	40.58	40.40	45
$(C_2H_5)_2NP(S)Cl_2$**	63 (1)	1.5262	1.2673	49.93	49.64	35
$[(CH_3)_2N]_2P(S)Cl$***	M. p. 22	—	—	—	—	40
$CH_3[(CH_3)_2N]P(S)Cl$****	103—105 (15)	1.5381	1.2488	39.44	39.30	31
$CH_3[(C_2H_5)_2N]P(S)Cl$*****	68—69 (2)	1.5242	1.1450	49.62	49.54	18

* Literature data [6]: b.p. 77.5° (10 mm), n_D^{20} 1.5390, d_4^{20} 1.3731.

** Found %: C 23.3, 23.2; H 4.6, 4.7; P 15.1, 15.0. $C_4H_{10}NPSCl_2$. Calculated %: C 23.3; H 4.9; P 15.0.

*** Literature data [3]: m.p. 22°.

**** Found %: P 19.6, 19.4. C_3H_9NPSCl. Calculated %: P 19.6.

***** Found %: P 16.9, 16.8. $C_5H_{13}NPSCl$. Calculated %: P 16.7.

b) Ethyl dichlorodithiophosphate was prepared from O-ethyl dichlorothiophosphate under conditions similar to those described above. Yield 25%; b.p. 64-66° at 3 mm, n_D^{20} 1.5890.

2. Treatment of aryl dichlorophosphates with phosphorus pentasulfide. A mixture of 0.1 mole of the aryl dichlorophosphate and 0.025 mole of P_2S_5 was heated in a current of nitrogen at 140-150° for 6 hr, after which the reaction mass was filtered and the filtrate distilled in the range 100-120° at 8 mm. The distillate was washed with cold water, diluted with ether, and dried over anhydrous sodium sulfate; then the ether was removed, and the residue was distilled in vacuo. The following compounds were obtained in this way.

O-Phenyldichlorothiophosphate; yield 45%.

B.p. 107-107.5° (8 mm), d_4^{20} 1.4095, n_D^{20} 1.5738; MR_D 53.14; calc. 52.98. Literature data [4]: b.p. 119-120°, d_4^{20} 1.40593.

O-p-Tolyl dichlorothiophosphate; yield 53%.

B.p. 91-92° (3 mm), d_4^{20} 1.3575, n_D^{20} 1.5615, MR_D 57.55; calc. 57.60.

Found %: C 34.6, 34.4; H 2.9, 2.9; P 12.9, 12.9. $C_7H_7OPSCl_2$. Calculated %: C 34.5; H 2.9; P 12.8.

3. Treatment of diaryl chlorophosphates and triaryl phosphates with phosphorus pentasulfide. A mixture of 0.1 mole of the diaryl chlorophosphate (or triaryl phosphate) and 0.025 mole of P_2S_5 was heated in a current of nitrogen at 140-150° for 6 hr, after which the hot reaction mass was filtered; the filtrate crystallized after cooling with solid carbon dioxide. The reaction products were purified by boiling with animal charcoal in alcoholic solution, recrystal-

lization from alcohol, and drying in vacuo. In all cases a mixture test with known samples gave no melting-point depression. Yields and constants of the resulting diaryl chlorothionophosphates and triaryl thionophosphates are given in Table 1.

4. Treatment of phosphoric and methanephosphonic acid amidochlorides with phosphorus pentasulfide. A mixture of 0.1 mole of phosphoric or methanephosphonic acid amidochloride and 0.025 mole of P_2S_5 was heated in a current of nitrogen at 160-170° for 10-12 hr. Then the entire liquid part was distilled from the reaction mixture in vacuo, washed with cold water, diluted with ether, and dried with anhydrous sodium sulfate; the ether was removed, and the residue was distilled in vacuo. Yields and constants of the resulting thiophosphoric and methanethiophosphonic acid amidochlorides are given in Table 2.

5. Methanephosphonic acid dimethylamidochloride. This was prepared in the usual way from methanephosphonyl chloride and dimethylamine; yield 74%.

B.p. 88-89° (10 mm), d_4^{20} 1.2152, n_D^{20} 1.4698; MR_D 32.48; calc. 32.78.

Found %: C 25.5, 25.3; H 6.8, 6.9; P 22.0, 21.7. C_2H_9ONPCl. Calculated %: C 25.3; H 6.8; P 21.8.

SUMMARY

1. The interaction of phosphorus pentasulfide with alkyl- and arylphosphoryl chlorides, triaryl phosphates, and phosphoric and methanephosphonic acid amidochlorides, as well as the complete amides of phosphoric and methanephosphonic acids, was investigated.

2. It was shown that treatment of arylphosphoryl chlorides, triaryl phosphates, and phosphoric and methanephosphonic acid amidochlorides with phosphorus pentasulfide leads to the corresponding thiono derivatives, while in the analogous reaction with ethyl dichlorophosphate a mixture is formed, apparently consisting of ethyl thiono-, thiol-, and dithiophosphates; replacement of oxygen with sulfur in the complete amides of phosphoric and methanephosphonic acids does not take place on heating with phosphorus pentasulfide.

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CERTAIN DERIVATIVES OF XANTHIC ACIDS

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In searching for efficient selective reagents for the flotation of cementation copper [1], dialkyldixanthides (Ia-d), alkoxymethyl butylxanthates (IIa-c) and carbomethoxy butylxanthate (III) were synthesized.

Dialkyldixanthides (Ia-d) are long-known compounds with a wide field of practical application (vulcanization of rubber [2], insecticidal [3] and repellent [4] action, modification of the emulsion polymerization of styrene [5], etc.). They are prepared by oxidation of the corresponding xanthates by various oxidizing agents [6], particularly sodium nitrite in an acid medium [7] (proceeding from a freshly-prepared aqueous solution of the xanthate). We distilled all four of the synthesized dixanthides, without decomposition, by using a rather high vacuum.

$\left(ROC\begin{matrix}S\\ \diagup\\ \diagdown\\ S\end{matrix}\right)_2$, where a) $R = CH_3$; b) $R = C_2H_5$; c) $R = n.\text{-}C_4H_9$; d) $R = n.\text{-}C_6H_{13}$.

(I)

Alkoxymethyl butylxanthates (IIa-c) were synthesized [taking into account their somewhat greater water-solubility (due to the presence of the ether oxygen atom) relative to the simple alkyl esters] through the interaction of potassium butylxanthate in acetone solution with chloromethyl methyl, chloromethyl ethyl, and chloromethyl butyl ethers [8].

$C_4H_9OC\begin{matrix}S\\ \diagup\\ \diagdown\\ S-CH_2OR\end{matrix}$, where a) $R = CH_3$; b) $R = C_2H_5$; c) $R = n.\text{-}C_4H_9$.

(II)

In order to obtain even more hydrophilic xanthate esters, an attempt was made to prepare butylxanthate esters containing a hydroxyl group by substituting α-glycol chlorohydrins for chloromethyl alkyl ethers; on the basis of these considerations ethylene and propylene chlorohydrins were brought into the reaction, and individual substances were isolated; on analysis of the latter, however, it was found that they were entirely devoid of oxygen and contained only carbon, hydrogen, and sulfur. On studying the literature in the light of these facts it was found that α-oxides, α-sulfides, and α-chlorohydrins react with xanthates [9] or with carbon disulfide in a methanolic-alkali medium [10] to form alkylene trithiocarbonates. Actually, in our case, instead of the expected hydroxyalkyl butylxanthates, the isolated substances proved to be ethylene and propylene trithiocarbonates: The first of these was identified through a mixture test with a sample of known ethylene trithiocarbonate synthesized from sodium trithiocarbonate and ethylene bromide [11]; the second was identified by comparing its constants with those of a sample prepared by countersynthesis through an analogous reaction (from 1,2-dibromopropane instead of ethylene bromide), and elementary analysis of the former.

Carbomethoxyl xanthate (III) was prepared through the reaction of potassium butylxanthate with methyl chloroformate at a reduced temperature. Under these conditions, however, a by-product was obtained—dimethyl thiodiformate $CH_3OCOSCOOCH_3$ (IV), which simultaneously may be regarded as the thioanhydride of monomethyl carbonate; the formation of such a compound is quite regular, since (III) in turn is a mixed thioanhydride of butylxanthic acid and monomethyl carbonate. The structure of (III) was proved by converting it to butylxanthanilide,*

* According to literature data [12] carbethoxyl ethylxanthate reacts with two molecules of aniline to form $C_6H_5NHCSSCONHC_6H_5$.

Dialkyldixanthides ROC(S)SS(S)COR

R	Melting point	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated
CH_3	22.5—23°[a]	104—106° (0.5)[b]	—	—	—	—
C_2H_5	31.5[c]	107—108 (0.2)[d]	—	—	—	—
n-C_4H_9	—	134—135 (0.35)	1.1518[e]	1.5800[f]	86.10	86.49
n-C_6H_{13}	—	149—152° (0.35)[g]	1.0897	1.5711[h]	104.49	104.96

Note. Literature data: [a]22-23 [14], 22.5-23 [7], 23-23.5 [6, 15]; [b]90-94 (0.1 mm [6]); [c]31-32 [14], 31.5-32 [7], 31.5-32.5 [6], 32.5 [15]; [d]107-109 (0.05 mm) [6]; [e]1.1562 [7], 1.1598 [14]; [f]1.5810 [7]; 1.5858 [14]; [g]170-175 (3 mm), slight decomposition [15]; [h]n_D^{25} 1.5569 [15]; the refraction for S_4 in dixanthides is taken to be 39.22 (8.11 for disulfide sulfur and 10.50 for thiocarbonyl sulfur) [16].

$C_4H_9OCSNHC_6H_5$; (IV) was identified by the absence of a melting-point depression in a mixture test with a sample prepared by the reaction of methyl chloroformate with sodium sulfide.

Of the substances described above, (III) is the one most active as a collector of cementation copper in flotation [13]. The authors thank A. K. Livshits for manifest interest in the present work.

EXPERIMENTAL

I. Dialkyldixanthides. To a mixture of 1 equiv. of the alcohol and 1 equiv. of concentrated aqueous sodium hydroxide solution, 1 equiv. of distilled carbon disulfide was added, the temperature being kept below 30°. The reaction mixture was stirred for 30 min more and cooled, and a concentrated aqueous solution of 1.1 equiv. of sodium nitrite was added; then the temperature was reduced to -3-0°, and 25% sulfuric acid was added until an acid reaction to Congo was obtained. The yellow oil was separated, the water layer extracted twice with ether, the ethereal extract added to the oil, the latter dried with magnesium sulfate, the ether driven off, and the dixanthide distilled in vacuo.

II. Alkoxymethyl butylxanthates. Methoxymethyl ester. To a solution of 9.4 g (0.05 mole) of potassium butylxanthate in 120 ml of acetone, 4.43 g (0.055 mole) of chloromethyl methyl ether was added. The mixture was heated for 2 hr to 60°, filtered, the acetone distilled from the filtrate, and the residue washed with water, dried with magnesium sulfate, and distilled twice; 6 g (63%) of the ester.

B.p. 79° (1.5 mm), d_4^{20} 1.0955, n_D^{20} 1.5258, MR_D 54.43; calc. 54.40.

Found %: C 43.01, 43.13; H 7.32, 7.40; S 32.79, 32.71. $C_7H_{14}O_2S_2$. Calculated %: C 43.26; H 7.26; S 33.03.

Ethoxymethyl ester. Similarly to the preceding, 18.8 g (0.1 mole) of potassium butylxanthate and 10.4 g (0.11 mole) of chloromethyl ethyl ether in 250 ml of acetone (70°, 2 hr) gave 11.4 g (55%) of the substance.

B.p. 93-94.5° (1.5 mm), d_4^{20} 1.0665, n_D^{20} 1.5179, MR_D 59.18; calc. 59.02.

Found %: S 30.89, 31.00. $C_8H_{16}O_2S_2$. Calculated %: S 30.77.

n-Butoxymethyl ester. The original chloromethyl n-butyl ether was prepared [8] from 225 g of technical formalin and 202 g of n-butyl alcohol. Yield 172.1 g (51%); b.p. 132° (743 mm); literature data [17]: b.p. 134° (760 mm).

An 18.8 g quantity (0.1 mole) of potassium butylxanthate and 13.5 g (0.11 mole) of chloromethyl butyl ether in 250 ml of acetone gave 13.9 g (59%) of the ester.

B.p. 108.5-110.5° (1.5 mm), d_4^{20} 1.0307, n_D^{20} 1.5090, MR_D 68.47; calc. 68.26.

Found %: S 26.98, 26.91. $C_{10}H_{20}O_2S_2$. Calculated %: S 27.13.

III. Interaction of potassium butylxanthate with α-chlorohydrins. Condensation of potassium butylxanthate with ethylene chlorohydrin. A mixture of 20.25 g (0.103 mole) of potassium butylxanthate and 8.28 g (0.103 mole) of ethylene chlorohydrin in 70 ml of acetone was boiled for 6 hr. After removing the acetone and then distilling the residue three times there was isolated a substance with b.p. 111-113° (0.8 mm), which completely crystallized on standing. M.p. 34.5-35.5° (from 70% alcohol).

Ethylene trithiocarbonate. To a saturated aqueous solution of 48 g (0.2 mole) of sodium sulfide, 18.25 g (0.24 mole) of carbon disulfide was added. The mixture was stirred at room temperature for 8 hr, and then the water was completely distilled off in vacuo (bath temperature not over 60°). To the residue, dissolved in 140 ml of dry alcohol, 29 g (0.155 mole) of ethylene bromide was added, and the mixture was boiled for 6 hr; after distilling off the alcohol the residue was extracted several times with ether. The ether was removed, after which the oil, which separated on cooling, completely crystallized. Yield 11.1 g (65%); m.p. 35-36° (from 70% alcohol). Literature data: m.p. 36-37° (from a benzene-petroleum ether mixture [10]), 36.5° (from an alcohol-ether mixture [11]). A sample mixed with a known specimen, melted at the same temperature.

Condensation of potassium butylxanthate with propylene chlorohydrin. A mixture of 14.2 g (0.15 mole) of propylene chlorohydrin and 28.5 g (0.15 mole) of potassium butylxanthate in 100 ml of acetone was boiled for 6 hr, cooled, filtered, the solvent driven off, and the residue distilled twice; 5.9 g (52%) of the substance was isolated.

B.p. 105-107° (0.7 mm), d_4^{20} 1.3427.*

Found %: C 32.09, 32.15; H 4.19, 4.25; S 63.64, 63.70. $C_4H_6S_3$. Calculated %: C 31.96; H 4.02; S 64.02.

Propylene trithiocarbonate. Similarly to the method of synthesis of ethylene trithiocarbonate, 96 g (0.4 mole) of crystalline sodium sulfide, 36.5 g (0.48 mole) of carbon disulfide, and 63.2 g (0.31 mole) of 1,2-dibromopropane were caused to react, and propylene trithiocarbonate was isolated. B.p. 95-96° (0.3 mm), d_4 1.3441. Literature data [9]: b.p. 136° (0.2 mm).

IV. Reaction of potassium butylxanthate with methyl chloroformate. To a solution of 47 g (0.25 mole) of potassium butylxanthate in 250 ml of acetone, 28.3 g (0.3 mole) of methyl chloroformate was gradually added at 0°, the mixture was stirred for 30 min at 20-30°, and the solvent and excess methyl chloroformate were distilled off in vacuo in a water bath. The residue was treated with 150 ml of a 1 : 1 water-ether mixture, and then the ether layer was washed with water, dried with magnesium sulfate, and the ether distilled off. The residue weighed 33.1 g. On fractionation in vacuo the main substance isolated was carbomethoxyl butylxanthate (III).

B.p. 70-72° (0.35 mm), d_4^{20} 1.1345, n_D^{20} 1.5220, MR_D 54.73; calc. 54.41.

Found %: S 30.49, 30.67. M 200, 204. $C_7H_{12}O_3S_2$. Calculated %: S 30.79, M 208.

A small amount of dimethyl thiodiformate (IV) was simultaneously isolated from the forerun of (III).

B.p. 69.5-70° (5 mm), m.p. 36°.

Found %: S 21.69, 21.47. M 152, 152. $C_4H_6O_4S$. Calculated %: S 21.36. M 150.

Butylxanthanilide. To 1.04 g (5 mM) of (III) in 15 ml of alcohol, 1.16 g (12.5 mM) of freshly-distilled aniline was added, the mixture being water-cooled; the latter was left overnight and then treated with an excess of 3% hydrochloric acid solution. The crystals which separated were filtered out, washed with water, and recrystallized three times from 50% alcohol. M.p. 52°. Literature data [18] m.p. 51-53°.

Found %: C 63.05, 63.16; H 7.45, 7.40; S 15.33, 15.24. $C_{11}H_{15}ONS$. Calculated %: C 63.15; H 7.23; S 15.33.

Dimethyl thiodiformate (IV). To a suspension of 39 g (0.5 mole) of anhydrous sodium sulfide in 90 ml of acetone, 113.4 g (1.2 moles) of methyl chloroformate was added (temperature not over 30°). The mixture was boiled for 2 hr, filtered, the residue washed with acetone, the solvent driven from the combined filtrate, and the residue distilled. Yield 18.8 g (25%), b.p. 65-67° (2 mm), m.p. 36°. A mixture test with a sample of (IV) did not give a melting-point depression.

SUMMARY

1. The fact of conversion of α-chlorohydrins to alkenyl trithiocarbonates on treatment with xanthates, was confirmed.

2. Alkoxymethyl and carbomethoxyl butylxanthates and dimethyl thiodiformate, which have not been described before, were synthesized.

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SYNTHESIS OF THIAZOLIDONE DERIVATIVES OF BIOLOGICAL INTEREST

XIV. THIAZOLIDONE DERIVATIVES WITH A CONDENSED IMIDAZOLE RING AND THEIR HYDROLYSIS

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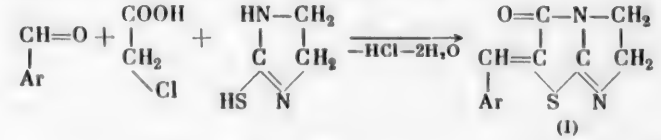
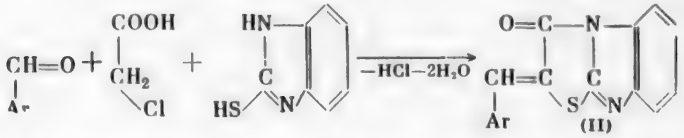
Original article submitted May 5, 1960

Stephen and Wilson [1] attempted to prepared thiazolidone derivatives with a condensed imidazole ring through the interaction of ethylenethiocarbamide and 2-mercaptobenzimidazole with ethyl chloroacetate in anhydrous alcohol in the presence of sodium ethoxide. In this case they obtained ethyl 4,5-dihydroimidazole- and benzimidazole-2-thioglycolates, respectively; the first substance could not be converted to a lactam, whereas the second was converted to a pseudothiohydantoin derivative only in trace amounts. In earlier articles [2] it was shown that the condensation of thiocarbamide or thiosemicarbazones with chloroacetic acid in the presence of aromatic aldehydes gives 5-arylidene derivatives of pseudothiohydantoin, usually in good yields.

In this view of this we carried out the condensations of ethylenethiocarbamide and 2-mercaptobenzimidazole with chloroacetic acid in the presence of aromatic aldehydes and sodium acetate, and thus obtained 5-arylidene derivatives of pseudothiohydantoin with condensed rings (I) and (II) in good yields and in one step (Table 1).

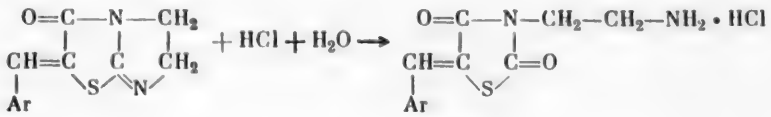


(I)



(II)

Of the various methods of preparing thiazolidinedione-2,4 derivatives, the most widely used is acid hydrolysis of pseudothiohydantoin [2,3]. On hydrolysis of monocyclic pseudothiohydantoins substituted in position 2', ammonia or an amine is simultaneously formed. The hydrolysis of bicyclic and tricyclic pseudothiohydantoins has not been studied as yet; however, physiologically active thiazolidinediones-2,4, in which the substituents in position 3 contain amino groups, must be formed in this reaction. On hydrolysis of pseudothiohydantoins, synthesized by condensation of chloroacetic acid with ethylenethiocarbamide and aromatic aldehydes, derivatives of 3-aminoethylthiazolidinedione-2,4 (III) are obtained in good yields (Table 2).



(III)

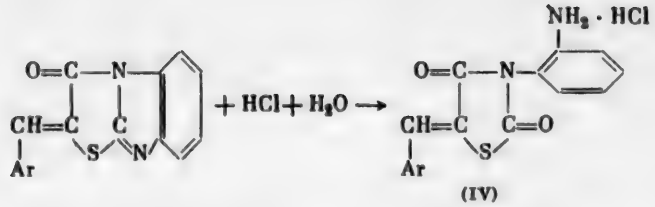
Hydrolysis of the products of condensation of chloroacetic acid with aromatic aldehydes and 2-mercaptobenzimidazole led to the formation of derivatives of 3-o-aminophenylthiazolidinedione-2,4 (IV) (Table 2).

TABLE 1.

Compound	Yield (in %)	Melting point	Found (%)			Molecular formula	Calculated (%)		
			C	H	N		C	H	N
(I), Ar = C_6H_5	96.5	280°	62.13	4.48	12.15	$C_{12}H_{10}ON_2S$	62.58	4.37	12.16
(I), Ar = p-$CH_3OC_6H_4$	57.6	258	59.56	4.86	11.16	$C_{13}H_{12}O_2N_2S$	59.98	4.64	10.71
(I), Ar = $C_6H_5CH=CH$	29.2	172	65.47	4.82	10.73	$C_{14}H_{12}ON_2S$	65.60	4.72	10.93
(I), Ar = p-$O_2NC_6H_4$	80.6	243	52.01	3.61	15.56	$C_{12}H_9O_3N_3S$	52.35	3.29	15.27
(I), Ar = o-$HOOCC_6H_4$	76.5	188	56.40	4.15	9.99	$C_{13}H_{10}O_3N_2S$	56.92	3.67	10.21
(II), Ar = C_6H_5	18.0	214	68.86	3.95	10.18	$C_{16}H_{10}ON_2S$	69.05	3.62	10.06
(II), Ar = o-HOC_6H_4	34.0	178	65.28	3.72	9.56	$C_{16}H_{10}O_2N_2S$	65.29	3.42	9.52
(II), Ar = $C_6H_5CH=CH$	54.7	234	71.10	4.11	9.14	$C_{18}H_{12}ON_2S$	71.03	3.97	9.20
(II), Ar = $CH_3CONHC_6H_4$	26.9	172	64.39	4.04	12.34	$C_{18}H_{13}O_2N_3S$	64.47	3.90	12.53
(II), Ar = m-$O_2NC_6H_4$	62.0	230	60.32	2.85	12.85	$C_{16}H_9O_3N_3S$	59.44	2.80	13.00
(II), Ar = β-$HOC_{10}H_6$	58.1	236	69.61	3.66	7.55	$C_{20}H_{12}O_2N_2S$	69.75	3.51	8.13
(II), Ar = p-$CH_3OC_6H_4$	51.9	230	65.99	4.02	9.22	$C_{17}H_{12}O_2N_2S$	66.22	3.92	9.08
(II), Ar = p-$O_2NC_6H_4$	37.1	280	59.36	3.06	12.94	$C_{16}H_9O_3N_3S$	59.43	2.80	13.00

TABLE 2.

Compound	Yield (in %)	Melting point	Found (%)			Molecular formula	Calculated (%)		
			C	H	N		C	H	N
(III), Ar = C_6H_5	27.0	274°	50.33	4.61	9.75	$C_{12}H_{13}O_2N_2SCl$	50.61	4.60	9.83
(III), Ar = $C_6H_5CH=CH$	27.8	225	54.23	5.08	9.26	$C_{14}H_{15}O_2N_2SCl$	54.10	4.86	9.01
(III), Ar = p-$CH_3OC_6H_4$	73.1	272	49.41	4.98	8.95	$C_{13}H_{15}O_3N_2SCl$	49.60	4.80	8.90
(III), Ar = o-$HOOCC_6H_4$	40.0	85	47.44	3.89	8.87	$C_{13}H_{13}O_4N_2SCl$	47.50	3.98	8.52
(IV), Ar = C_6H_5	20.9	180	57.38	4.11	8.93	$C_{16}H_{13}O_2N_2SCl$	57.74	3.93	8.41
(IV), Ar = $C_6H_5CH=CH$	75.1	204	60.16	4.33	7.86	$C_{18}H_{15}O_2N_2SCl$	60.25	4.21	7.80
(IV), Ar = o-HOC_6H_4	53.2	240	54.55	3.56	8.06	$C_{16}H_{13}O_3N_2SCl$	55.09	3.75	8.03
(IV), Ar = p-$O_2NC_6H_4$	77.0	256	51.24	3.46	11.24	$C_{16}H_{12}O_4N_3SCl$	50.87	3.20	11.12



(IV)

The ultraviolet absorption spectra of bicyclic pseudothiohydantoins (I) (2-arylidene derivatives of 1-thia-4,7-diazabicyclo[8-4]octen-7-one-3) (Fig. 1) consists of two bands – a short-wave amido band and a long-wave K-band [4]. The maxima in the amido band are weak, go over to inflections, or are entirely absent [only the p-nitrobenzylidene derivative has a maximum (259 mμ) in this band]. However, maxima (319-355 mμ) in the K-band, due to the presence of the conjugated chain Ar – CH = C – C = O, are very pronounced. Introduction of an o-carboxyl group into the benzylidene grouping leads to shifting of the maximum from 238 to 319 mμ. On the other hand, the p-nitro and p-methoxyl groups shift the maximum toward longer wavelengths (by 18 and 23 mμ, respectively).

The absorption spectra of tricyclic pseudothiohydantoins (II) (12-arylidene derivatives of 1-thia-3,10-diazatricyclo[4-9; 2-10]dodecene-2-aren-4-one-11) consist of three bands (Figs. 2 and 3) – the amido (257-273 mμ) and benzimidazole (281-296 mμ) bands and the K-band (319-390 mμ). A pronounced maximum in the benzimidazole band (285 mμ) occurs in the case of benzimidazole-S-thioglycolic acid lactam and a number of its 5-arylidene derivatives. The benzimidazole absorption band is very intense and, being situated in the immediate vicinity of the K-band, strongly affects that band. In certain cases the K-band is very weak (p-acetamidobenzylidene, m-nitrobenzylidene, p-methoxybenzylidene, and p-nitrobenzylidene derivatives). Introduction of the o-hydroxyl group into the benzylidene grouping leads to shifting of the maximum toward shorter wavelengths.

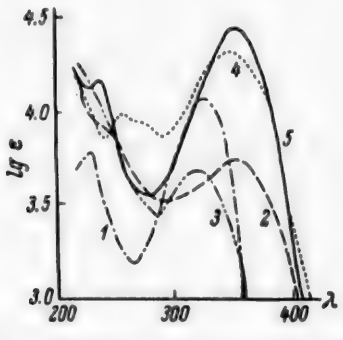


Fig. 1. Absorption spectra of compounds (I). 1) Benzylidene derivative; 2) cinnamylidene derivative; 3) o-carboxybenzylidene derivative; 4) p-methoxybenzylidene derivative; 5) p-nitrobenzylidene derivative.

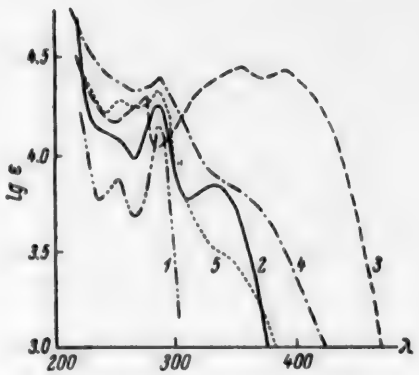


Fig. 2. Absorption spectra of benzimidazole-S-thioglycolic acid lactam and compounds (II). 1) Lactam; 2) salicylidene derivative; 3) cinnamylidene derivative; 4) p-nitrobenzylidene derivative; 5) m-nitrobenzylidene derivative.

The absorption spectra of derivative of 3-β-aminoethylthiazolidinedione-2,4 consist of two bands [4] – the amido band and the K-band (Fig. 4). In all cases the K-band has a pronounced maximum in the 311-358 mμ region; however, the maximum in the amido band (240-256 mμ) is not always pronounced, and sometimes goes over to an inflection (the o-carboxybenzylidene derivative).

The o-carboxyl group, which was introduced into the benzylidene grouping, causes an appreciable (14 mμ), hypsochromic shift of the K-band maximum similar to that for pseudothiohydantoins. However, the p-methoxyl group causes a 25 mμ bathochromic shift. It should be noted that the p-methoxyl group has the opposite effect on the amido band causing a 16 mμ hypsochromic shift of the maximum in this band.

The absorption spectra of derivatives of 3-o-aminophenylthiazolidinedione-2,4 (Fig. 5) differ considerably from the spectra of (III). The C_6H_5 group in position 3, bound to the amido group, causes a bathochromic shift of

the amido band. The maximum in this band (275-290 mμ) is pronounced. On the other hand, the maxima in the K-band practically vanish and go over into inflections in the 320-360 mμ region. The 5-cinnamylidene derivative, in whose molecule the conjugation chain is the longer Ar − CH = CH − CH = C − C = O, which causes a marked maximum (325 mμ) to appear in the K-band, is an exception.

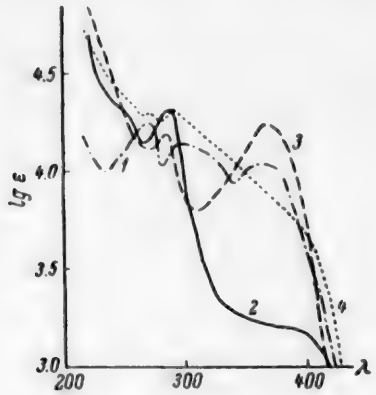


Fig. 3. Absorption spectra of compounds (II). 1) Benzylidene derivative; 2) p-acetamidobenzylidene derivative; 3) hydroxynaphthalidene derivative; 4) p-anisylidene derivative; 5) m-nitrobenzylidene derivative.

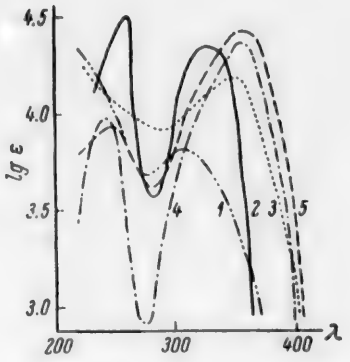


Fig. 4. Absorption spectra of 3-aminoethylthiazolidinediones-2,4 (III). 1) o-Carboxybenzylidene derivative; 2) benzylidene derivative; 3) p-nitrobenzylidene derivative; 4) cinnamylidene derivative; 5) p-anisylidene derivative.

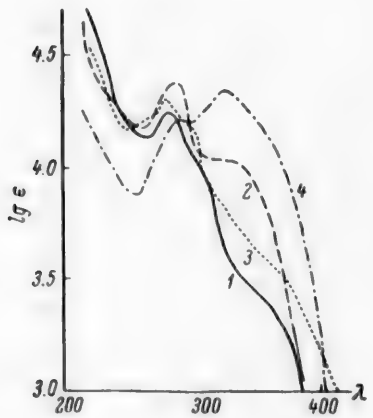


Fig. 5. Absorption spectra of 3-aminophenylthiazolidinediones-2,4 (IV). 1) Benzylidene derivative; 2) o-carboxybenzylidene derivative; 3) p-nitrobenzylidene derivative; cinnamylidene derivative.

Substances with antispasmodic and hypotensive activity were found among the compounds synthesized.*

EXPERIMENTAL

Pseudothiohydantoins. A 20-50 mM quantity of ethylenethiocarbamide or 2-mercaptobenzimidazole was dissolved in 30-60 ml of glacial acetic acid and boiled with equimolar quantities of chloroacetic acid, and aromatic aldehyde, and crystalline sodium acetate for 2-3 hr. After cooling, the mixture was diluted with water, and the reaction product was filtered out, washed with water, and recrystallized from alcohol, dioxane, or acetic acid, with the exception of the 5-benzylidene derivative (I), which was crystallized from water. The synthesized substances (Table 1) consisted of white or yellow crystals soluble on heating in acetic acid and insoluble in ether. The 5-arylidene derivatives (I) dissolved, as a rule, on heating in water and alcohol.

Thiazolidinediones. A 2-10 mM quantity of the pseudothiohydantoin derivative was refluxed in a flask with 20-150 ml of concentrated hydrochloric acid for 4-20 hr. The solution was filtered, if necessary, and evaporated to dryness in a water bath. The residue was purified by recrystallization from alcohol or washing with organic solvents.

The hydrochlorides of 5-arylidene-3-β-aminothiazolidinediones-2,4 (III) consisted of white crystals soluble on heating in water, alcohol, and glacial acetic acid. They were practically insoluble in chloroform, ether, and acetone. The hydrochlorides of 5-arylidene-3-o-aminophenylthiazolidinediones-2,4 (IV) consisted of crystals nearly insoluble in water and most organic solvents. They were readily soluble on heating in glacial acetic acid.

* The investigations were conducted in the Pharmacology Department, L'vov Medical Institute, under the direction of A. A. Gavrilyuk.

The spectra were taken with an SF-4 spectrophotometer. Solutions were prepared in ethanol (1-2 mg in 100 ml).

SUMMARY

1. On condensation of chloroacetic acid with ethylenethiocarbamide (or 2-mercaptobenzimidazole) in the presence of aromatic aldehydes, pseudothiohydantoins with a condensed imidazole ring are formed in good yields.

2. On acid hydrolysis of pseudothiohydantoins with a condensed imidazole ring, derivatives of 3-β-aminoethyl- and 3-o-aminophenylthiazolidinediones-2,4 are obtained.

3. The ultraviolet absorption spectra of the substances obtained, consist of amido (maxima at 240-290 mμ) and conjugated (311-390 mμ) bands. In the case of tricyclic pseudothiohydantoins there is also the benzimidazole band (maximum at 281-296 mμ).

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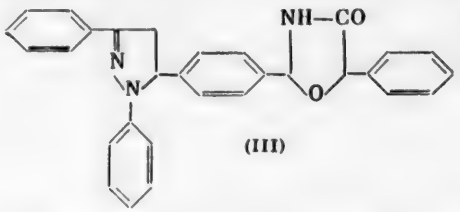
SYNTHESIS OF LUMINESCENT HETEROCYCLIC COMPOUNDS

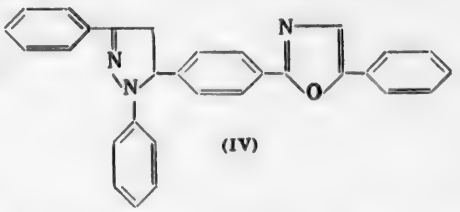
E. E. Baroni and K. A. Kovyrzina

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 5,
pp. 1641-1643, May, 1961
Original article submitted June 7, 1960

It is well known that in plastic scintillators not only 2,5-diphenyloxazole, but also 1,3,5-triphenyl-Δ^2-pyrazoline has high scintillation efficiency [1]. In the development and extension of work done earlier [2], the synthesis of the following combined heterocyclic systems was worked out: 1-[1,3-diphenyl-Δ^2-pyrazolinyl-(5)]-4-[5-phenyloxazolidonyl-(2)]-benzene (III) and 1-[1,3-diphenyl-Δ^2-pyrazolinyl-(5)]-4-[5-phenyloxazolyl-(2)]-benzene (IV).

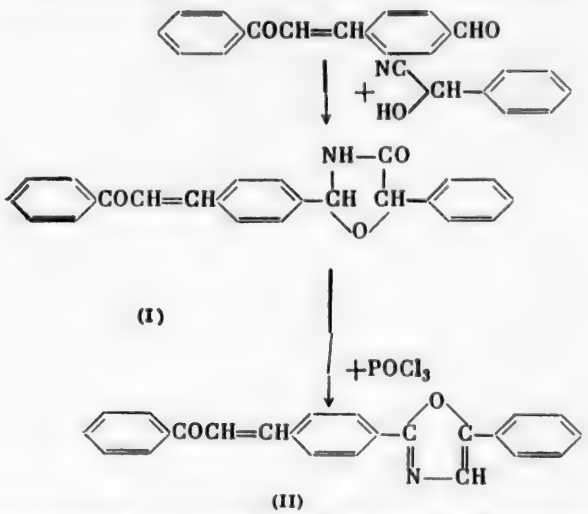


(III)



(IV)

The starting material for the synthesis of (III) and (IV) was p-(3-phenylpropen-1-one-3)benzaldehyde, which is obtained as a result of the condensation of terephthalic aldehyde with acetophenone [3]. The closing of the oxazolidone and oxazole rings was carried out analogously to methods for preparing oxazolidone and oxazole, known in the literature [4]. Two new luminescent organic compounds, (III) and (IV), were prepared by treatment of (I) and (II), respectively, with phenylhydrazine according to the usual method of preparing Δ^2-pyrazoline derivatives [5].



(II)

On irradiation with ultraviolet both substances display an intense, blue fluorescence both in the crystalline state and in organic solvents. The scintillation efficiency of the given compounds was reported in a separate article [6]; the hypothesis originally advanced has been confirmed.

EXPERIMENTAL

1-[3-Phenylpropen-1-one-3]-4-[5-phenyloxazolidonyl-(2)]-benzene (I). Two g of p-(3-phenylpropen-1-one-3)benzaldehyde (m.p. 124°) was dissolved in a dioxane-absolute ether mixture (1 : 1), and 1.2 g of freshly-prepared mandelonitrile was added to the solution. Then dry hydrogen chloride was passed into the clear, faintly-yellowish solution at 0°. The precipitate, which formed on the walls of the flask, was filtered out after 1 hr, and treated with with boiling alcohol. The undissolved white, crystalline precipitate (I) was filtered out while hot.

M.p. 193-194° (from xylene); yield 2.3 g (73.3%).

Found %: C 78.36; H 4.92. M 360. $C_{24}H_{19}O_3N$. Calculated %: C 78.03; H 5.18, M 365.40.

1-[3-Phenylpropen-1-one-3]-4-[5-phenyloxazolyl-(2)]-benzene (II). One g of (I) and 10 ml of phosphoryl chloride were heated in a water bath for 0.5 hr. The resulting clear solution was cooled, the phosphoryl chloride was distilled off, with slight heating, in a water-jet-pump vacuum, and the solid residue was dissolved in ether containing 1% HCl. The white, crystalline precipitate formed was filtered out, and used without purification for further synthesis.

1-[1,3-Diphenyl-Δ^2-pyrazolinyl-(5)]-4-[5-phenyloxazolidonyl-(2)]benzene (III). A 0.9 g quantity of (I) in 40 ml of glacial acetic acid was heated nearly to boiling, and 0.45 g of phenylhydrazine was added to the solution with stirring. The suspension immediately turned bright-red, and the solid phase quickly dissolved. Then a nearly-colorless precipitate began to form rapidly. The color of the solution in this case gradually shifted toward orange. Heating was continued for 1 hr. Then the reaction mass was cooled, and the precipitate was dried by suction and washed on the filter with acetic acid.

The product was insoluble in alcohol and acetone, but soluble in benzene and more soluble in pyridine. On heating in benzene both precipitate and solution became bright-red; decomposition probably took place. A perfectly pure substance was obtained after chromatographic purification on alumina. M.p. 202° (decomp.). The substance displayed an intense, blue-violet fluorescence both in the crystalline state and in solutions.

Found %: C 78.5; H 5.52; N 8.95. M 457. $C_{30}H_{25}O_2N_3$. Calculated %: C 78.41; H 5.48; N 9.14. M 459.52.

1-[1,3-Diphenyl-Δ^2-pyrazolinyl-(5)]-4-[5-phenyloxazolyl-(2)]benzene (IV). An 0.87 g quantity of (II) was dissolved by heating in 40 ml of glacial acetic acid, and 0.4 ml of phenylhydrazine was added to the clear solution with stirring. The reaction mass was heated to 90-100° for 2 hr. When the solution had cooled, the grayish-brown precipitate formed was dried by suction, and a benzene solution of it was purified chromatographically on alumina. The product was a colorless, crystalline substance having a blue-violet fluorescence both in the crystalline state and in organic solvents. M.p. 194° (decomp.).

Found %: C 81.23; H 5.69; N 9.15. M 445.5. $C_{30}H_{23}ON_3$. Calculated %: C 81.60; H 5.19; N 9.51. M 441.5.

SUMMARY

Methods were developed for synthesizing new luminescent organic substances containing two heterocyclic rings: Δ^2-pyrazoline and oxazole, and Δ^2-pyrazoline and oxazolidone.

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SYNTHESIS OF γ-CARBOXYBUTYROLACTONES

I. OXIDATION OF α-SUBSTITUTED γ-CHLOROALLYLACETIC ACIDS BY HYDROGEN PEROXIDE IN ACETIC ANHYDRIDE

M. T. Dangyan and G. M. Shakhnazaryan

Erevan State University

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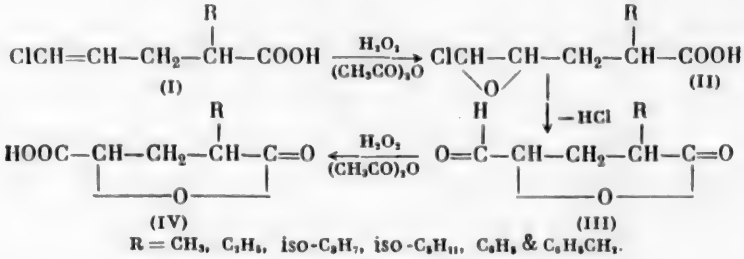
pp. 1643-1647, May, 1961
Original article submitted May 6, 1960

Butyrolactone derivatives, particularly α-substituted γ-carboxybutyrolactones, have been little studied, and at present there is no method for their preparation. In 1925 Ingold [1] first prepared α-methyl-γ-carboxybutyrolactone together with γ-carboxy-γ-valerolactone through the reaction of α-methylglutaric acid with halogens. In 1928 α-isopropyl-γ-carboxybutyrolactone was prepared through the oxidation of α-phellandrene to α-isopropyl-δ-oxo-γ-caprolactone and subsequent reaction of the latter with sodium hypobromite [2]. This lactone and its ethyl ester were prepared in 1946 by oxidizing δ-hydroxy-γ-valerolactone with chromic anhydride [3]. In the preceding work [4] we found that the oxidation of alkyl-γ-chloroallylacetic acids with hydrogen peroxide in an acetic acid medium at 60-70° gives α-alkyl-γ-hydroxyglutarolactones in 58-70% yields.

In the present investigation we sought to extend the developed method of preparing α-alkyl-γ-carboxybutyrolactones to other substituted γ-chloroallylacetic acids. It was found that yields of reaction products were increased 10-20% by carrying out the oxidation in an acetic anhydride medium. Hence it follows that the yields of α-substituted γ-carboxybutyrolactones depend on the concentration of hydrogen peroxide or peracetic acid. Moreover, it was found that increasing the quantity of hydrogen peroxide in the reaction mixture from 2 : 1 to 4 : 1 promotes an increase in the yields of α-substituted γ-carboxybutyrolactones. Further increase in the quantity of hydrogen peroxide does not affect the yields. The oxidation of substituted γ-chloroallylacetic acids with hydrogen peroxide is also of great interst from the theoretical point of view, since in this case [4] two concurrent reactions of oxidation of (I) and (III) take place.



R = CH_3, C_2H_5, iso-C_3H_7, iso-C_5H_{11}, C_6H_5 & $C_6H_5CH_2$.

Naturally, (III) is oxidized far more readily than (I), and hence as a result we have not aldehydolactones (III), but carboxylactones (IV). However, it may be possible to obtain aldehydolactones in the presence of inhibitors. Work in this direction is in progress. The formation of succinic acid derivatives on oxidation is also possible, but was observed only in the oxidation of γ-chloroallylacetic acid. The formation of substituted succinic acids in the oxidation of substituted γ-chloroallylacetic acids, was not observed. The results of numerous experiments provide grounds for assuming that the oxidation of γ-chloroallylacetic acid probably goes according to the following scheme.

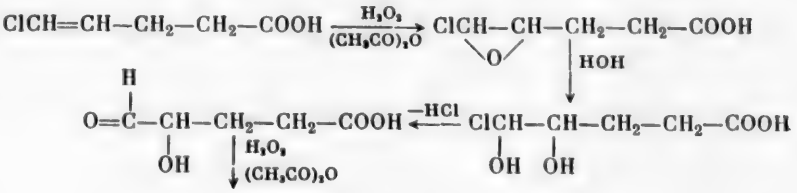
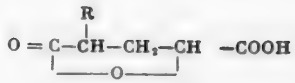


TABLE 1.

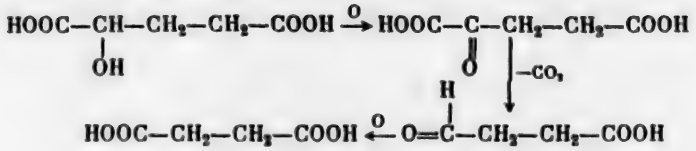


R	Quantity of starting materials: acid (in g)	acetic anhydride (in ml)	hydrogen peroxide (in ml)	Temperature	Time (in hr)	Yield (in %)	Boiling point (pressure in mm)	Melting point	Molecular formula	% C: found	% C: calc.	% H: found	% H: calc.	Titration (phenolphthalein) with sodium hydroxide: sample wt. (in g)	found: in the cold	found: on heating	calc.
CH_3	10	60	27	60—65°	18	61.8	175—80° (10 мм)*	—	$C_6H_8O_4$	—	—	—	—	—	—	—	—
C_2H_5	10	46	25	60—70	24	75	168—72 (5)	83—85	$C_7H_{10}O_4$	52.87	53.16	6.70	6.33	0.1053	0.11 N., 6.3 ml	0.11 N., 5.9 ml	0.11 N., 12.7 ml
iso -C_3H_7	10	50	24	60—70	20	66	165—7 (4)	60—62**	$C_8H_{12}O_4$	—	—	—	—	—	—	—	—
iso -C_5H_{11}	10	45	23	55—65	25	74	—	102—103	$C_{10}H_{16}O_4$	59.70, 59.53	60.00	7.92, 8.03	8.00	0.1424	0.1087 N., 6.5 ml	0.1087 N., 6.36 ml	0.1087 N., 13.04 ml
C_6H_5	10	45	22	65—75	16	63.8	—	125—127	$C_{11}H_{10}O_4$	64.25, 64.27	64.08	5.27, 5.36	4.85	0.0980	0.1087 N. 4.6 ml	0.1087 N. 4.2 ml	0.1087 N. 8.76 ml
$C_6H_5CH_2$	14.1	60	30	65—70	24	70.7	218—20 (5)***		$C_{12}H_{12}O_4$	64.88, 64.93	65.35	4.94, 4.91	5.15	0.1300	0.085 N. 5.1 ml	0.085 N. 5.26 ml	0.085 N. 10.68 ml

*According to literature data [1]: b.p. 185-187 (14 mm).

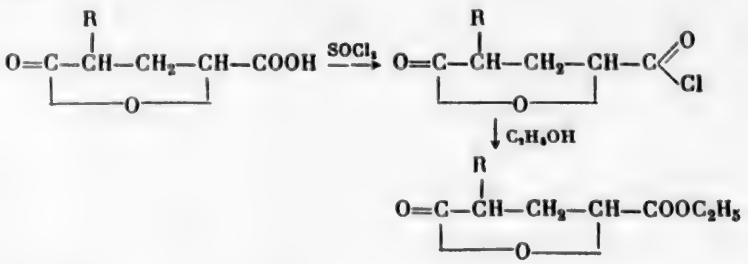
**According to literature data [3]: m.p. 58-60° 97-98.

***n_D^{20} 1.5465, d_D^{20} 1.2793. Found MR_D 54.49. $C_{12}H_{12}O_4F_3$. Calculated 54.89.



Presumably, since γ-chloroallylacetic acid is unsubstituted in the α-position, its oxidation goes not through the stage of aldehydolactone formation but probably through γ-hydroxyglutaric monoaldehyde which under the experimental conditions is not converted to the lactone but is further oxidized, similarly to α-glycols. In the contrary case the formation of succinic acids would be observed even on oxidation of substituted γ-chloroallylacetic acids. Thus the absence of a radical in the α-position causes a change in the direction of oxidation.

In the present work the oxidation of propyl-, isobutyl-, and all other alkyl(aryl)-γ-chloroallylacetic acids, was carried out in an acetic anhydride medium, which led to higher yields than those obtained earlier in acetic acid. All compounds obtained, except α-methyl- and α-benzyl-γ-carboxybutyrolactones, are white, crystalline substances insoluble in water and soluble in most organic solvents. The presence of free and bound carbosyl groups was proved by titration with alkali in the cold and on heating. The presence of a free carboxyl group was confirmed also by preparation of the ethyl esters.



The presence of a bound carboxyl group in esterolactones was proved by titration with alkali on heating.

EXPERIMENTAL

α-Alkyl(aryl)-γ-chloroallylacetic acid, 28% hydrogen peroxide, and acetic anhydride were put into a three-neck round-bottom flask provided with a mechanical stirrer, a reflux air condenser, and a thermometer extending to the bottom of the flask. The mixture was stirred until the initially-formed emulsion disappeared; this was accompanied by evolution of heat (cooling was sometimes necessary). After the mixture became homogeneous, the stirring could be stopped and the mixture heated for 18-25 hr, the temperature being kept at 60-75°. Then the acetic acid water were distilled off at reduced pressure. The crystalline product was recrystallized from benzene, carbon tetrachloride, ether, n-hexane, or a benzene-petroleum ether mixture. In the case of a liquid product it was fractionated in vacuo. The hydrogen peroxide was used in 4-fold excess, whereas the acetic anhydride was used in the proportion that would give 42-48% hydrogen peroxide.

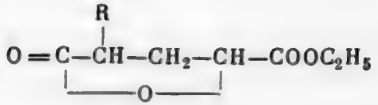
The rest of the experimental conditions and the properties of the compounds obtained, are given in Table 1.

α-Alkyl(aryl)-γ-carboxybutyrolactones were very soluble in ether, alcohol, dioxane, boiling carbon tetrachloride, and boiling benzene and slightly soluble in petroleum ether, n-hexane, and water.

Oxidation of γ-Chloroallylacetic Acid. A mixture of 10 g of γ-chloroallylacetic acid, 40 ml of acetic anhydride, and 25 ml of 28% hydrogen peroxide was stirred until a homogeneous solution was obtained, and then was heated at 55-65° for 20 hr. After fractionation in vacuo there was obtained 3.5 g of a substance distilling at 175-180° (8-9 mm). The product consisted of white crystals with m.p. 181-183° (from water). The melting point of succinic acid is 184.5-185°. A mixture test with a known sample gave no melting-point depression.

α-Alkyl(aryl)-γ-carbethoxybutyrolactones. Into a 100-ml round-bottom flask, provided with a reflux condenser, were put 0.05 mole of the α-alkyl(aryl)-γ-carboxybutyrolactone and 8-10 ml of thionyl chloride, and the mixture was heated in a water bath for 25-30 min. After this the excess thionyl chloride was driven off, and 15-20 ml of

TABLE 2.



R	Yield (in %)	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Molecular formula	% C found	% C calc.	% H found	% H calc.	Titration (phenolphthalein) with sodium hydroxide: sample wt. (in g).	found on heating	calc.
CH_3	65	134—138° (14)*	1.4495	1.1431	40.39	40.26	$C_8H_{12}O_4$	55.67, 55.58	55.81	6.87, 7.12	7.00	—	—	—
C_2H_5	76	118—125 (4—5)	1.4502	1.1169	44.76	44.87	$C_9H_{14}O_4$	58.23, 58.07	58.06	7.26, 7.34	7.52	0.1034	0.1087 N 5.5 ml	0.1087 N 5.2 ml
iso -C_3H_7**	72	150—153 (26)	1.4471***	—	—	—	$C_{10}H_{16}O_4$	—	—	—	—	—	—	—
iso -C_5H_{11}	73.5	138—142 (4)	1.4550	1.040	59.47	58.92	$C_{12}H_{20}O_4$	63.48, 63.55	63.16	9.13, 8.90	8.77	0.1770	0.0787 N 9.5 ml	0.0787 N 9.84 ml
C_6H_5	69.2	182—186 (8—9)	1.5119	1.1664	60.18	59.76	$C_{13}H_{14}O_4$	66.25, 66.17	66.66	5.67, 5.89	5.98	0.4950	0.0787 N 26.40 ml	0.0787 N 26.66 ml
$C_6H_5CH_2$	66.7	171—173 (5)	1.5066	1.1611	63.65	64.23	$C_{14}H_{16}O_4$	67.81	67.77	6.30	6.48	0.0966	0.1087 N 7.4 ml	0.1087N 7.05 ml

* According to literature data [1]: b.p. 170-172° (14-15 mm).

** According to literature data [3]: b.p. 150.5-152° (26 mm), n_D^{24} 1.4469.

*** Determined at 24°.

anhydrous alcohol was added to the residue, the mixture being cooled; then the mixture was heated in a water bath for about 3 hr. After driving off the alcohol, the residue was distilled in vacuo.

The constants of the α-alkyl(aryl)-γ-carbethoxybutyrolactones and data of elementary analyses are given in Table 2.

SUMMARY

1. On oxidation of alkyl(aryl)-γ-chloroallylacetic acids with hydrogen peroxide in an acetic anhydride medium, the corresponding α-alkyl(aryl)-γ-carboxybutyrolactones were obtained in 61.8-75% yields.

2. It was shown that under these conditions, only γ-chloroallylacetic acid is not converted to the lactone. It is further oxidized, succinic acid being formed.

3. α-Alkyl(aryl)-γ-carbethoxybutyrolactones were prepared.

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COMPOUNDS OF TIN CHLORIDE AND BROMIDE WITH ANILINE

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Translated from Zhurnal Obshchei Khimii Vol. 31, No. 5,
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Compounds of tin chloride and bromide with two molecules of aniline are described in the literature [1,2]. The composition of these compounds corresponds to the coordination number of tin, i.e. six. It was established [2] that pink prismatic crystals containing excess aniline are precipitated from a solution of $SnCl_4 \cdot 2C_6H_5NH_2$ in aniline. The suggestion was made that the addition of excess aniline takes place in the outer sphere of the complex as a result of the strengthening of the acid function of the amino group of aniline, located in the inner sphere. Since the inner sphere of the complex contains two molecules of aniline, the outer sphere can add one or two molecules of aniline. It may be assumed that tin bromide also gives similar compounds with aniline.

The task of the present investigation was to obtain compounds of tin chloride and bromide with aniline, containing more than two molecules of aniline. For this purpose we first attempted to obtain compounds of tin chloride with three and four molecules of aniline.

EXPERIMENTAL

Preliminarily cooled solutions of $SnCl_4$ and $C_6H_5NH_2$ in benzene were carefully mixed (with cooling) in the appropriate ratios; colorless precipitates were formed, filtered, washed repeatedly with hot benzene, dried and analyzed for the tin and chlorine contents. Tin was determined gravimetrically as SnO_2, chlorine was titrated by the Volhard method.

Found %: Sn 22.46, 22.16; Cl 26.36, 26.72. $SnCl_4 \cdot 3C_6H_5NH_2$. Calculated %: Sn 21.99; Cl 26.26.

Found %: Sn 21.81, 22.10; Ci 27.17, 27.27. $SnCl_4 \cdot 4C_6H_5NH_2$. Calculated %: Sn 18.77; Cl 28.43.

From the analytical data it is evident that when tin chloride is mixed with aniline in a ratio of 1 : 3 or 1 : 4, the same compound, $SnCl_4 \cdot 3C_6H_5NH_2$, is precipitated.

When the compound is allowed to stand, it turns light-pink. When this compound is heated, it first becomes wet and turns yellow; then, when the $C_6H_5NH_2$ has volatilized, it again becomes a dry pink powder, which sublimes (at about 205°) with partial decomposition, without melting. The sublimate is colorless. The analysis of the sublimate obtained by heating the compound $SnCl_4 \cdot 3C_6H_5NH_2$ is as follows:

Found %: Sn 26.22, 26.23; Cl 32.48, 31.61. $SnCl_4 \cdot 3C_6H_5NH_2$. Calculated %: Sn 21.99; Cl 26.26. $SnCl_4 \cdot 2C_6H_5NH_2$. Calculated %: Sn 26.57; Cl 31.74.

Therefore, when the compound $SnCl_4 \cdot 3C_6H_5NH_2$ is heated, a molecule of aniline is first removed, and the compound $SnCl_4 \cdot 2C_6H_5NH_2$ then sublimes.

Since a compound containing only one excess molecule of aniline was obtained with tin chloride, only mixtures with a component ratio of 1 : 3 were prepared with tin bromide. When the solutions were mixed we obtained a precipitate which was treated in a similar way.

Found %: Sn 16.06, 15.98; Br 44.17, 44.06. $SnBr_4 \cdot 3C_6H_9NH_2$. Calculated %: Sn 16.54; Br 44.54.

From the analytical data it is evident that the compound formed had the composition $SnBr_4 \cdot 3C_6H_5NH_2$. It was a slightly yellowish powder. When heated, it also split off aniline and partially volatilized, together with aniline. The dry residue sublimed in the form of fine yellow crystals.

Found %: Br 51.34, 51.56. $SnBr_4 \cdot 2C_6H_5NH_2$. Calculated %: Br 51.17.

Thus, like $SnCl_4 \cdot 3C_6H_5NH_2$, when the compound $SnBr_4 \cdot 3C_6H_5NH_2$ was heated, one molecule of aniline was removed and the compound with two molecules of aniline, $SnBr_4 \cdot 2C_6H_5NH_2$ then sublimed.

The addition of the third molecule of aniline to the complex compound $SnX_4 \cdot 2C_6H_5NH_2$ takes place in the outer sphere of the complex as a result of the strengthening of the acid function of the NH_2 group of the aniline present in the inner sphere, i.e. the compound $SnX_4 \cdot 2C_6H_5NH_2$ acts as a monobasic complex acid with respect to aniline.

The structure of the compounds $SnX_4 \cdot 3C_6H_5NH_2$ may be represented as follows:

$$\left[SnX_4 \begin{matrix} C_6H_5NH_2 \\ C_6H_5NH \end{matrix}\right]^- \cdot C_6H_5NH_3^+.$$

SUMMARY

1. The compounds $SnCl_4 \cdot 3C_6H_5NH_2$ and $SnBr_4 \cdot 3C_6H_5NH_2$ were obtained. When heated, both compounds lose one molecule of aniline and sublime, without melting, in the form of compounds with two molecules of aniline: $SnX_4 \cdot 2C_6H_5NH_2$.

2. The system of the structure of the compounds $SnX_4 \cdot 3C_6H_5NH_2$ is given; according to this, the third molecule of aniline is added in the outer sphere as a result of the acid-base reaction of the complex $SnX_4 \cdot 2C_6H_5NH_2$ with excess aniline.

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RADICAL EXCHANGE IN ORGANOMETALLIC COMPOUNDS

V. THE PROBLEM OF THE MECHANISM OF THE EXCHANGE REACTION*

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The report of Calingaert and his co-workers [1] established that radical exchange takes place in organolead compounds and that the exchange reaction takes place only in the presence of various addition agents [2]. However, no mechanism was proposed for the explanation of the exchange reaction. When the exchange of ethyl radicals in the system tetraethyl lead – ethyl bromide was investigated it was established [3] that even heating for 20 hours at 140° does not lead to such exchange. But heating the initial substances in the presence, for example of ferric chloride, aluminum chloride and bromide leads to exchange, reaching 20% in this period. It was suggested that the mechanism of the exchange reaction consists in the formation of an intermediate complex of both components of the system and the addition agents. Owing to lack of experimental data it was not possible to suggest a reliable structure for the intermediate complex.

Continuing the investigation of the properties of the organometallic compounds, we studied the exchange of ethyl radicals in the system triethylaluminum – ethyl bromide [4]. It was established that, in this case, exchange is absent when the initial substances are heated. In the presence of bismuth, copper and iron halides at 100°, exchange reached 100% in 15-20 hours. Therefore, the presence of additions of metal halides in the system is a necessary condition for radical exchange. Experimental data [3,4] show an increase in the degree of exchange when metal halides of variable valence, for example, $FeCl_3$, CuCl, $CuCl_2$ and $CoCl_2$ and also halides of metal-acceptors $AlCl_3$ and $AlBr_3$ are used.

On the basis that cyclic complexes may exist [5,6], we assume that radical exchange in tetraethyl lead – ethyl bromide and triethylaluminum – ethyl bromide systems takes place via the formation of a six-membered cyclic active complex (I) in which rupture (crossed lines) and "nascent" (dotted lines) bonds, possibly of the following structure, alternate:

$$R_nMe' + \overset{\bullet}{R}Hal + Me''RHal_n \rightleftharpoons R_{n-1}Me' \begin{matrix} \diagup R \cdots Hal \\ \diagdown \overset{\bullet}{R} \cdots Hal \end{matrix} Me''Hal_{n-1} \rightleftharpoons R_{n-1}Me'\overset{\bullet}{R} + RHal + Me''Hal_n \quad (I)$$

By way of addition agents, we employed metal halides with d-electrons in their orbits. Proximity of the s-, p- and d-levels is characteristic of elements with d-electrons. As a result, mutual transfers of electrons between the s-, p- and d-orbits are possible, with an increase in the number of "loose" electrons. For example, the following transfers are possible in the case of the Fe atom: 4s → 4p, 3d → 4p, transfer of 2 electrons in succession from the 3d level to the 4p level being possible. Similar transfers are also possible for other elements, for example Cu, Co and Ni. In the basic states, Fe, Co and Ni have two paired s-electrons. Transfer of one of these to the d-nucleus requires 20, 10 and 0.6 kcal respectively [7]. From the point of view of energy, such transfers of electrons are, therefore, perfectly possible. Unpairing of the electrons leads to a higher valence, and as a result, additional bonds to the main valence bonds may appear; this leads to the reaction of the apparently "saturated" molecules with each other. The particular feature of such additional or so-called donor-acceptor bonds is that they increase the number of valence bonds between atoms by attracting the electrons of the donor atom and those of the free orbits of the acceptor atom [8].

On the basis of the above it may be assumed that a donor-acceptor bond, leading to the formation of a molar compound $RHal\cdots MeHal_n$, is established between the alkyl halide and the metal halide. It is known that molecular

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compounds are strongly polarized and have a high dipole moment [7]. Polarization of the molecular compound weakens the R--Hal covalent bond. This, together with the presence of an empty orbit in the aluminum atom in triethylaluminum, makes possible the formation of a six-membered cyclic complex. The absence of an empty orbit in the lead atom of tetraethyl lead impedes the formation of a cyclic complex, and there is negligible exchange of ethyl radicals in the system tetraethyl lead – ethyl bromide under fairly severe conditions.

The cyclic complex is in equilibrium with the initial and final products. Since the old bonds have already been broken and the new bonds have not yet been firmly established, rupture of both types of bonds is possible. If the "nascent" bonds are ruptured, the initial products are re-obtained. But if the old bonds are broken, new products, formed as a result of exchange, are obtained. A labeled radical of the alkyl halide migrated into the initial organometallic compound, while one of the radicals of the initial organometallic compound formed a molecule of alkyl halide by combining with the halogen of the addition agent.

To obtain a more accurate picture of the mechanism of the exchange reaction, it would be of interest to investigate the effect of the solvent on the degree of exchange. It should be noted that some organometallic compounds form stable complexes with the solvent.

Since tetraethyl lead does not form complexes with such solvents as nitromethane and dimethyl formamide, their positive effect on the degree of exchange is explained by the subsequent polarization of the cyclic complex and, therefore, the subsequent loosening of its bonds, which assists an increase in the degree of exchange. Data obtained during an investigation of the effect of ether as a solvent on the degree of exchange in the system triethylaluminum – ethyl bromide are of interest. The Table gives only the maximum time of the exchange reaction and the degree of exchange corresponding to this time at one of the investigated temperatures.

Effect of Solvent on Ethyl Radical Exchange in the System $Al(C_2H_5)_3 - C_2H_5Br$ at 100°

Addition agent	Solvent	Time (hours)	Degree of exchange	$K \cdot 10^5$ (sec^{-1})
$BiCl_3$	—	15	0.88	8.82
$BiCl_3$	Ether	15	0.16	0.0724
$FeCl_3$	—	20	0.87	6.13
$FeCl_3$	Ether	20	0.13	0.0406

The experimental data corroborate that the presence of an empty orbit in the Al atom in triethylaluminum assists the formation of a cyclic complex. But if the empty orbit of the Al atom is occupied, the formation of the complex will be markedly impeded. Ether occupies this empty orbit of the Al atom in triethylaluminum by forming a donor-acceptor bond between the atom of the oxygen donor and the empty orbit of the atom of the aluminum-acceptor electrons. As a result, there is a marked reduction in the velocity constant of the exchange reaction (120-150-fold) in ether compared with the exchange reaction without a solvent. Other solvents which form complexes with triethylaluminum, such as quinoline, pyridine, etc., will evidently have a similar effect on the degree of exchange in this system.

One characteristic is evident from an examination of the mechanism of an exchange reaction taking place via a cyclic complex, with alternation of rupturing and "nascent" bonds. If the proposed system (I) is correct, exchange of halogen between alkyl halide and the metal halide of the addition agent must be observed simultaneously with radical exchange. If a halogen-labeled metal halide is used as the addition agent, after exchange we must obtain an alkyl halide unlabeled with respect to carbon but halogen-labeled, which would be additional proof that a cyclic complex is formed. When experiments were carried out with halogen-labeled metal halides, only the qualitative aspect was of interest to us, i.e. would the alkyl halide contain a label at the halogen after the exchange reaction had been carried out. By way of labeled addition agents we used ferric chloride and silver chloride, labeled with chlorine-36. It was found that in actual fact, after exchange the alklyl halide had an activity of 50-160 counts/min, depending on the activity of the initial ferric chloride and silver chloride. At the same time, we carried out blank tests in which triethylaluminum, unlabeled ethyl bromide and labeled ferric chloride were placed in an ampoule and separated immediately. It was found that the alkyl halide did not contain a radioactive label. Therefore, experiments with labeled metal halides confirm the assumption that the exchange reaction takes place via the formation of a six-membered cyclic complex.

EXPERIMENTAL

Equimolecular (with respect to the radical) amounts of triethylaluminum and ethyl bromide, and also ferric chloride or silver chloride (as addition agent), labeled with chlorine-36 by a previously described method [4], were placed in an ampoule which was sealed and thermostatically controlled under predetermined conditions. After the exchange reaction had been carried out, the ethyl bromide was separated, together with the ethyl chloride (formed in small quantities). It is known that, being a strongly polar solvent, dimethylformamide (DMF) causes ionization of alkyl halides [9] even at room temperature; this makes it possible to separate a halide from a DMF-alkyl halide mixture in the form of silver halide. We made use of this feature of DMF. The opened reaction ampoule was connected to a vacuum line via an intermediate trap, cooled by liquid nitrogen. A quantity of 1 ml of DMF and 1 ml of 2 N silver nitrate solution were placed in the trap. The contents of the latter were then frozen and the ethyl bromide was pumped off from the reaction mixture by a current of air. During this process, the ethyl bromide and traces of ethyl chloride were frozen in the trap with DMF and the silver nitrate solution. The trap was then unfrozen and shaken vigorously for 15 minutes. A turbidity first appeared, and a copious precipitate of silver chloride was then formed. The silver chloride was filtered, washed repeatedly with water, dried and a sample was prepared. The radiochemical analysis was carried out with a Geiger-Müller counter.

The ferric chloride, labeled with chlorine-36, was obtained by the Erdman [10] method, by chlorination of iron filings. The chlorine-36 for chlorination was obtained by reacting labeled hydrochloric acid with permanganate. The silver chloride, labeled with chlorine-36, was obtained by reacting labeled hydrochloric acid with silver nitrate.

SUMMARY

1. A reaction mechanism for radical exchange in organometallic compounds in the presence of halides of certain metals was proposed and discussed.

2. An explanation was given for the influence of complex-forming solvents on the degree of exchange in the system $Al(C_2H_5)_3 - C_2H_5Br$ in the presence of metal halides.

3. Experiments were carried out to confirm the proposed mechanism, using two labeled compounds in the same exchange reaction.

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FLUOROMETHYL ESTERS OF SULFURIC ACID

IV. DIFLUORO- AND TETRAFLUORODIMETHYL SULFATES

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In previous communications [1] the preparation of a number of fluoromethyl esters of sulfuric acid by the electrochemical fluorination of sulfuric acid derivatives were examined. We assumed that fluorine-containing sulfates could also be obtained by the reaction of sulfur trioxide with the corresponding fluorinated ethers. It is known that dimethyl [2], chlorodimethyl [3], sym dichlorodimethyl [3], diethyl [4] and di-β-chloroethyl sulfates [5] were prepared in this way; at the same time it was reported that dipropyl and di-γ-chloropropyl sulfates were not obtained.

The present communication describes the reaction of sulfur trioxide with 1,1-difluoromethyl ether obtained from difluorochloro methane and sodium methylate [6]. It was found that the reaction of difluorodimethyl ether with sulfur trioxide or its solutions in inert solvents takes place only at a temperature of about +20°, and in the case of combined sulfur trioxide, for example 60% oleum or dioxan-sulfotrioxide, at a higher temperature.

In all cases the reaction product is 1,1-difluorodimethyl sulfate, the yield being about 50%.

$$CHF_2OCH_3 + SO_3 \longrightarrow CHF_2OSO_2OCH_3$$

The structure of this compound was proven by the fact that when a sample of the preparation was dissolved in aqueous alkali only 3 equiv. were consumed, 1 equiv. of carbon monoxide was liberated and 2 equiv. of fluorine ion were detected in the solution; the sulfate ion was detected only after the alkaline solution had been heated or after long standing, which agrees with the known fact of the stability of methylsulfuric acid and its salts in aqueous and weakly alkaline aqueous solutions [7].

$$CHF_2OSO_2OCH_3 + 3NaOH \longrightarrow CO + 2NaF + NaOSO_2OCH_3 + 2H_2O$$

When methyldifluoromethyl sulfate is heated above 60°, it decomposes, liquid and gaseous products being formed. Carbon monoxide and hydrogen fluoride are found in the gaseous products; the methyl ester of fluorosulfonic acid, tetrafluorodimethyl sulfate and dimethyl sulfate are present in the liquid products. The formation of these products is evidently explained by the decomposition of methyldifluoromethyl sulfate.

$$CHF_2OSO_2OCH_3 \begin{cases} \nearrow FSO_2OCH_3 + CO + HF \\ \searrow (CHF_2O)_2SO_2 + (CH_3O)_2SO_2 \end{cases}$$

The structure of symmetrical tetrafluorodimethyl sulfate was proven by the fact that when a sample of the preparation was dissolved in aqueous alkali, exactly 6 equiv. of alkali were consumed, 2 equiv. of carbon monoxide were liberated and 4 equiv. of the fluorine ion and 1 equiv. of the sulfate ion were detected in the solution.

$$(CHF_2O)_2SO_2 + 6NaOH \longrightarrow 2CO + 4NaF + Na_2SO_4 + 4H_2O$$

EXPERIMENTAL

Reaction of 1,1-difluorodimethyl ether with sulfur trioxide. A solution of 16 g of sulfur trioxide in 50 ml of chloroform was added slowly to a solution of 24 g of difluoromethyl ether in 150 ml of dry chloroform at 20°. The

temperature of the mixture rose slightly, carbon monoxide and hydrogen fluoride were liberated and the solution turned light-yellow. The mixture was left for 20 hours at room temperature and was then evaporated under reduced pressure. The residue (30.2 g of a dark-brown liquid) was fractionated twice under reduced pressure. We obtained 16.6 g of 1,1-difluorodimethyl sulfate with a b.p. of 47° (12 mm), d_4^{20} 1.6033, n_D^{20} 1.4262. The yield was 51.2%, calculated on the sulfur trioxide.

Found %: C 14.64, F 23.96; S 19.42. M 164.3. $C_2H_4O_4F_2S$. Calculated %: C 14.82; F 23.46; S 19.76. M 162.1.

1,1-Difluorodimethyl sulfate is a colorless liquid which darkens on standing and is soluble in the majority of organic solvents and aqueous alkalis. When a sample of the preparation was dissolved in 0.1 N caustic soda, 0.96 equiv. of carbon monoxide (by volume) was liberated, 3.02 equiv. of alkali were consumed and 1.96 equiv. of the fluorine ion were detected in the solution; after the alkaline solution had been boiled, the consumption of alkali reached 3.94 equiv. and 0.92 equiv. of the sulfate ion was detected in the solution.

Thermal decomposition of difluorodimethyl sulfate. A quantity of 16.2 g of difluorodimethyl sulfate was heated at 60-70° for 1 hour; the mixture turned brown and carbon monoxide (test with palladium chloride) and hydrogen fluoride were liberated. The reaction mixture was fractionated at a pressure of 10 mm; the following fractions were collected: 1st) -30-0°, 6.7 g; 2nd) 0-15°, 3.5 g; 3rd) 65-71°, 2.3 g; residue (black tar) 0.8 g. By repeated distillation of the 1st fraction we obtained the methyl ester of fluorosulfonic acid (b.p. 91-91.5° d_4^{20} 1.4236, n_D^{20} 1.3692.

Found %: C 20.83; H 2.47; F 17.04; S 27.63. M 116.0. CH_3O_3FS. Calculated %: C 21.07; H 2.63; F 16.67; S 28.08. M 114.0.

Repeated distillation of the 2nd fraction gave the symmetrical tetrafluorodimethyl sulfate with a b.p. of 36-37° (98 mm), d_4^{20} 1.5807, n_D^{20} 1.3385.

Found %: C 12.84; F 38.55; S 15.96. $C_2H_2O_4F_4S$. Calculated %: C 12.12; F 38.38; S 15.16.

When a sample of the preparation was dissolved in 0.1 N caustic soda, 2.07 equiv. of carbon monoxide were liberated, 6.06 equiv. of alkali were consumed and 4.06 equiv. of the fluorine ion and 0.97 equiv. of the sulfate ion were detected in the solution.

Repeated distillation of the 3rd fraction gave dimethyl sulfate b.p. 68.5-69.5° (10 mm), d_4^{20} 1.3328, n_D^{20} 1.3856. Literature data for dimethyl sulfate are: b.p. 69-70° (10 mm), d_4^{20} 1.33, n_D^{20} 1.3874.

SUMMARY

1,1-Difluoromethyl sulfate was obtained by reacting 1,1-difluorodimethyl ether with sulfur trioxide. The thermal decomposition of difluorodimethyl sulfate was investigated and symmetrical tetrafluorodimethyl sulfate was obtained.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESIS OF 4-HALOGO DERIVATIVES OF THE LACTAM OF 1-AMINO-8-NAPHTHOIC ACID (4-HALOGO NAPHTHOSTYRILS) BASED ON ACENAPHTHENE

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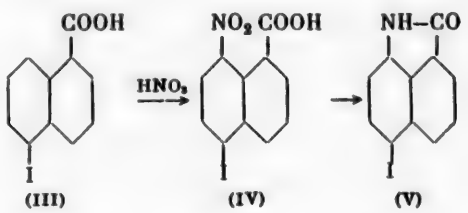
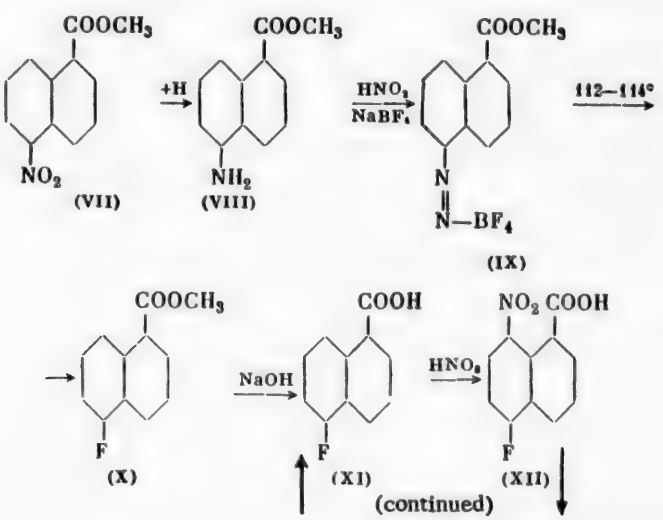
4-Chloro and 4-bromonaphthostyrils (I, II) were first obtained by reduction of the corresponding 5-halogo-8-nitro-1-naphthoic acids [1]. Subsequently, several methods for obtaining these compounds were described. Thus, 4-chloronaphthostyril was obtained by isomerization of N-chloronaphthostyril [2], chlorination of naphthostyril by chlorine in concentrated sulfuric acid, chlorination of the hydrochloride of 1-amino-8-naphthoic acid by a solution of sodium hypochlorite, and by the action of sulfuryl chloride on naphthostyril in tetrachloroethane [3] and acetic acid [4]. The same product was obtained with alkaline fusion of 5-chloro-1-cyanonaphthalene-8-sulfonic acid [5]. 4-Bromonaphthostyril was obtained by bromination of naphthostyril in acetic acid [4,6].

We established that these compounds and 4-iodonaphthostyril (V) may be obtained with good yields by halogenation of naphthostyril in an aqueous medium.

The structure of 4-iodonaphthostyril, which is not described in the literature, was proven by its synthesis from 5-iodo-1-naphthoic acid (III).



4-Fluoronaphthostyril (XIII), which is not described in the literature, was synthesized by us by several methods, as follows.



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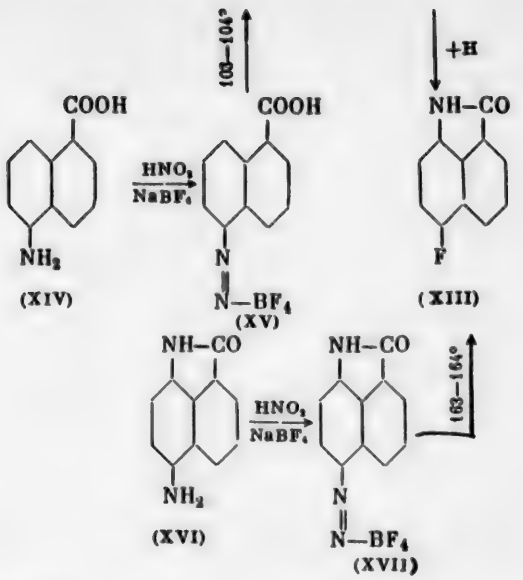
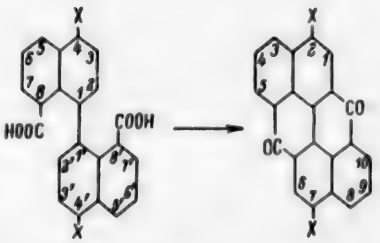


We obtained the same product (XIII) in all cases (a mixed sample gave no depression of the melting point).

All the 4-halogen naphthostyryls obtained were converted by diaryl condensation to the corresponding 1,1'-dinaphthyl-8,8'-dicarboxylic acids (XVIII-XXI), and the latter were converted to 2,7-dihalogen anthanthrones (XXII-XXV).



(XVIII) X = Cl; (XIX) X = Br; (XX) X = I; (XXI) X = F; (XXII) X = Cl; (XXIII) X = Br; (XXIV) X = I; (XXV) X = F.*

EXPERIMENTAL

4-Chloronaphthostyril (I). A quantity of 3.38 g of naphthostyril was ground to a paste with 5 ml of a 25% solution of hydrochloric acid, transferred to a flask equipped with a stirrer, and a further 30 ml of the same acid was added. Over a period of 10 minutes, 21 ml of sodium hypochlorite (according to Raschig) [7] was added to the solution obtained, the temperature being kept at +25-26°. The product obtained was filtered, washed with 300 ml of boiling water (to remove naphthostyril) and dried at 110-120°. We obtained 4.02 g of a substance with an m.p. 247-253°. When it was converted to 2,7-dichloroanthanthrone (XXII), the yield of the latter was 61.5% (calculated on the naphthostyril). The yield of (XXII) from pure (I) was 69%.

4-Bromonaphthostyril (II) A quantity of 45 ml of 15% sulfuric acid and 4.3 g of potassium bromide was added to a paste with 3.38 g of naphthostyril and 5 ml of the same acid. The mixture was heated to 25-26° and 1.15 g of potassium hypobromite in 20 ml of water was added to it with vigorous stirring in 5 minutes. We obtained 4.95 g of a product with an m.p. 236-239°. When it was converted to 2,7-dibromoanthanthrone (XXIII), the yield of the latter was 66.8%. The yield of (XXIII) from the pure substance (II) was 75%.

5-Iodo-8-nitro-1-naphthoic acid (IV). 5 g of 5-iodo-1-naphthoic acid (III), obtained by the Seer and Scholl method [8], was wetted with 5 ml of fuming nitric acid (d 1.5), stirred well for 2 minutes and then diluted immediately with water. The precipitate was filtered, washed with water and treated with 10 ml of a concentrated ammonia solu-

* The fluorine in the compounds obtained by the authors was determined in the Institute of Organic Chemistry, Academy of Sciences, Ukraine SSSR by L. M. Yagupol'skii, to whom we wish to express our sincere thanks.

tion with heating on a water bath. The ammonium salt of (IV), precipitated after cooling, was crystallized from acetic acid. We obtained 3.15 g of (IV) with an m.p. of 290-291° (with decomp.).

Found %: N 4.12, 4.21; I 36.87, 36.9. $C_{11}H_6O_4NI$. Calculated %: N 4.08; I 36.99.

4-Iodonaphthostyril (V). A saturated solution of iron sulfate was added to a solution of 2 g of (IV) in 50 ml of 28% ammonia until a black precipitate was formed. The precipitate was filtered and the filtrate was neutralized with hydrochloric acid and boiled for 5 minutes. The precipitate which came out on cooling was treated with a 6% solution of soda and washed with water. We obtained 1.4 g of (V) with an m.p. of 227-228°. After repeated crystallization from alcohol, yellow needles with an m.p. 232-233° were obtained.

Found %: N 4.82, 5.9; I 43.12, 43.21. $C_{11}H_6ONI$. Calculated %: N 4.75; I 43.01.

Preparation of 4-iodonaphthostyril (V) by direct iodination of naphthostyril. A quantity of 16.9 g of naphthostyril, 500 ml of water, 10 ml of nitric acid (d 1.43) and 15 g of well-ground iodine were added to a two-necked flask equipped with a stirrer and reflux condenser. The mixture was heated for 30 minutes at 40-50°, 30 minutes at 60-70°, 30 minutes at 85-95° and boiled for 15 minutes. The excess iodine was combined with a solution of sodium sulfate, the product was filtered, washed with boiling water and dried at 105-110°. We obtained 28.5 g of a yellow product with a m.p. of 220-223°. After recrystallization from 400 ml of 50% acetic acid, 26.6 g (90%) of a substance with a m.p. of 229-230° was obtained. After repeated crystallization the m.p. was 232-233°. A mixed sample with the product (V) showed no depression of the melting point.

Found %: N 4.92, 4.68; I 42.93, 43.00. $C_{11}H_6ONI$. Calculated %: N 4.75; I 43.01.

2,4-Diiodonaphthostyril (VI). A quantity of 1.69 g of naphthostyril was dissolved in 30 ml of acetic acid, diluted with 2.54 g of iodine and 0.37 g of iodic acid and boiled until all the iodine had disappeared. The product formed (VI) was precipitated in the form of yellow needles. We obtained 3.3 g with an m.p. of 260-262°. After recrystallization from alcohol the m.p. was 266-267°.

Found %: I 60.12, 60.02. $C_{11}H_5ONI_2$. Calculated %: I 60.29.

The structure of (VI) was proven by the fact that when the tetraiodo-1,1'-dinaphthyl-8,8'-dicarboxylic acid obtained from it was heated with concentrated sulfuric acid it was not converted to tetraiodoanthanthrone.

4,4'-Diiodo-1,1'-dinaphthyl-8,8'-dicarboxylic acid (XX). A quantity of 2.95 g of (V) was dissolved with boiling in 50 ml of a 6% caustic potash solution, cooled to room temperature and added slowly to 20 ml of 50% sulfuric acid. A solution of 0.8 g of sodium nitrite in 1.5 ml of water was added dropwise at -2° to the sulfate of 4-iodo-1-amino-8-naphthoic acid obtained, and the mixture was stirred for 30 minutes. The diazo solution was neutralized with 10% sodium carbonate until a weakly acid reaction to Congo Red, was obtained, and it was then poured into a solution containing 2.15 g of cuprous chloride, 1.35 g of sodium bicarbonate, 8 ml of 28% ammonia and 15 ml of water. After 0.5 hours the solution was filtered and the filtrate was acidified with sulfuric acid. The precipitate was treated with 50 ml of 10% soda with heating, refiltered and the filtrate was again acidified with sulfuric acid. The precipitate of (XX) was filtered and dried. The yield was 2.25 g (75.8%). It crystallized from acetic acid in the form of yellow needles it did not melt at 370°.

Found %: I 42.56, 42.84. $C_{22}H_{12}O_4I_2$. Calculated %: I 42.72.

2,7-Diiodoanthanthrone (XXIV). A quantity of 2.25 g of (XX) was heated for 1 hour with 30 ml of concentrated sulfuric acid at 40°. The solution obtained was poured into water, the precipitate was filtered and treated with 10% soda with heating. The dye was filtered and dried. The yield was 1.33 g (62.8%). The substance crystallized from nitrobenzene in the form of dark-red needles; it did not melt at 370°.

Found %: I 45.46, 45.32. $C_{22}H_8O_2I_2$. Calculated %: I 45.48.

The methyl ester of 5-nitro-1-naphthoic acid (VII) was obtained by the Eckstrand method [9].

Methyl ester of 5-amino-1-naphthoic acid (VIII). We dissolved 4.62 g of (VII) in 60 ml of 50% alcohol with heating on a water bath; 18 g of sodium hyposulfite was added to the solution and the product was heated for 40 minutes. The alcohol was distilled and the precipitated product was filtered. To purify the product, it was dissolved in dilute hydrochloric acid, the impurities were filtered, the solution of the hydrochloride was decomposed with ammonia, extracted with ether, the ethereal solution was dried with potash and was converted to the hydrochloride again by the

addition of gaseous hydrogen chloride. The yield of the hydrochloride was 3.2 g. From the hydrochloride we obtained free(VIII), which crystallized from alcohol in the form of yellow needles with an m.p. of 48-49°.

Found %: N 6.78, 6.87. $C_{12}H_{11}O_2N$. Calculated %: N 6.96.

Methyl ester of 5-fluoro-1-naphthoic acid (X). A solution of 1 g of sodium nitrite in 4 ml of water was added with stirring to a cooled (0°) mixture of 2 g of (VIII), 4 ml of concentrated hydrochloric acid and 4 ml of water. The reaction mixture obtained was stirred at 0° for 30 minutes and filtered. A cooled solution containing 6 g of sodium fluoboride in 6 ml of water was added to the filtrate. The greenish-yellow precipitate of the diazonium fluoboride of (IX) was filtered, washed with cold methanol and then with ether, and dried in a vacuum desiccator above calcium chloride. The yield was 2.82 g (94.0%). The decomp. temp. was 112-114°. After the decomposition of dry (IX), substance (X) was obtained. This was steam distilled; we obtained 1.6 g (83.7%) of colorless needles with an m.p. of 22°. The b.p. was 193-194° (753 mm).

Found %: F 9.18. $C_{12}H_9O_2F$. Calculated %: F 9.30.

5-Fluoro-1-naphthoic acid (XI) was obtained by saponification of (X) in an aqueous-alcoholic solution of caustic soda with boiling for 10-15 minutes. (XI) was precipitated from the alkaline solution by hydrochloric acid. It was in the form of yellow plates (from chlorobenzene); the m.p. was 213-214°.

Found %: F 9.52, 9.78. $C_{11}H_7O_2F$. Calculated %: F 9.99.

Preparation of 5-fluoro-1-naphthoic acid (XI) from 5-aminonaphthoic acid (XIV). This compound was obtained by the Eckstrand method [10]. We dissolved 6.71 g of the hydrochloride of (XIV) in 100 ml of 4% hydrochloric acid; the solution was cooled to -2° and diazotized with a solution of 2.3 g of sodium nitrite in 15 ml of water. The diazo solution was filtered and poured into a solution of 1.5 g of sodium fluoboride in 15 ml of water. The precipitate of the diazonium fluoboride of (XV) was filtered, washed with alcohol and ether and dried in a vacuum desiccator over calcium chloride. The yield was 6.8 g (79%). The decomp. temp. was 103-104°. The (XV) obtained was boiled with 100 ml of chlorobenzene until liberation of boron fluoride ceased; 5 g of activated carbon was added and boiling was continued for 30 minutes. The solution was filtered hot; after it had cooled, we obtained 3.2 g of (XI) with an m.p. of 210-211°. The pure acid melted at 213-214°.

Found %: F 9.81. $C_{11}H_7O_2F$. Calculated %: F 9.99.

5-Fluoro-8-nitro-naphthoic acid (XII). A quantity of 1.9 g (XI) was wetted with 3 ml of nitric acid (d 15), mixed well and diluted with water. The precipitate was filtered, washed well with water, transferred to a beaker and treated with a small quantity of 28% ammonia. The difficultly soluble ammonium salt which was formed was filtered and treated with dilute hydrochloric acid. The acid (XII) crystallized from chlorobenzene as yellow needles with an m.p. of 180-181°.

Found %: F 7.92, 8.12. $C_{11}H_6O_4NF$. Calculated %: F 8.08.

4-Fluoronaphthostyril (XII) was obtained in a similar way to (V). From 2.35 g of (XII) we obtained 1.35 g (72.2%) of (XIII); the latter was in the form of yellow needles with an m.p. of 252-253° (from alcohol).

Found %: F 9.98, 10.27. $C_{11}H_6ONF$. Calculated %: F 10.15.

Preparation of 4-fluoronaphthostyril (XIII) from 4-aminonaphthostyril (XVI). The latter was obtained according to [4]. A quantity of 6.62 g of the hydrochloride of (XVI) was dissolved in 60 ml of water and acidified with hydrochloric acid (2 ml, d 1.19). The solution obtained was cooled to -2° and diazotized with 2.3 g of sodium nitrite dissolved in 15 ml of water. After it had stood for half an hour it was filtered and a solution of 20 g of sodium fluoboride in 20 ml of water was added to the filtrate. After 1 hour the greenish-yellow precipitate of (XVII) diazonium fluoboride was filtered and dried at 105-110°. The yield of (XVII) was 5.71 g (67.3%). The decomp. temp. was 163-164°. After decomposition of the diazonium fluoboride the (XIII) obtained was extracted with alcohol, the alcoholic solution was boiled with activated carbon, filtered and the alcohol was evaporated until (XIII) crystallized. It was obtained as yellow needles with an m.p. of 252-253°.

Found %: F 10.42. $C_{11}H_6ONF$. Calculated %: F 10.15.

4,4'-Difluoro-1,1'-dinaphthyl-8,8'-dicarboxylic acid (XXI) was obtained in a similar way to (XX). From 1.87 g of (XIII) we obtained 1.55 g (82.0%) of (XXI). It was in the form of colorless needles (from acetic acid with an m.p. 315-316° (with decomp.).

Found %: F 9.89, 9.96. $C_{22}H_{12}O_4F_2$. Calculated %: F 10.04.

2,7-Difluoroanthanthrone (XXI) was obtained in a similar way to (XXIV). From 1.89 g of (XXI) we obtained 1.7 g (99.4%) of substance (XXV). It crystallized from nitrobenzene as orange needles; it did not melt at 370°.

Found %: F 10.67, 10.92. $C_{22}H_8O_2F_2$. Calculated %: F 11.10.

SUMMARY

1. It was shown that 4-chloro-4-bromo- and 4-iodonaphthostyril can be obtained by direct halogenation of naphthostyril in an aqueous medium.

2. The following compounds, which are not described in the literature were synthesized: 5-iodo- and 5-fluoro-8-nitro-1-naphthoic acids, 5-fluoro-1-naphthoic acid, the methyl esters of 5-amino- and 5-fluoro-1-naphthoic acid, 4-iodo-and 2,4-diiodonaphthostyrils, 4,4'-difluoro- and 4,4'-diiodo-1,1'-dinaphthyl-8,8'-dicarboxylic acids, and 2,7-difluoro- and 2,7-diiodoanthanthrones.

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THE SYNTHESIS OF HALOGEN-SUBSTITUTED UNSYMMETRICAL DERIVATIVES OF 1,6-DIPHENYLHYDRAZODITHIOCARBONAMIDE. IV

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We previously described the synthesis of unsymmetrical derivatives of 1,6-diphenylhydrazodithiocarbonamide [1,2]. In a number of compounds the presence of halogens and alkoxy groups causes the appearance (or intensification) of various antimicrobic properties [3,4], and it was therefore of interest to synthesize halogen derivatives of unsymmetrical 1,6-diaryl hydrazodithiodicarbonamide and investigate their properties. These derivatives were obtained, as before, by reacting substituted 4-phenylthiosemicarbazide with the corresponding substituted phenyl isothiocyanates with heating in anhydrous alcohol:

$$RNHCSNHNH_2 + R'NCS \rightarrow RNHCSNHNHCSNHR'$$

The 4-phenylthiosemicabazide derivatives were obtained from the corresponding substituted phenyl isothiocyanates and hydrazine hydrate in anhydrous alcohol [5]. Substituted phenyl isothiocyanates were synthesized from the corresponding amine and thiophosgene in chloroform and water [6]. The synthesized unsymmetrical halogen derivatives of 1,6-diphenylhydrazodithiodicarbonamide are given in the Table. As may be seen from the latter, unsymmetrical halogen derivatives of 1,6-diphenylhydrazodithiodicarbonamide are obtained with good yields, they decompose when melting, and crystallize from alcohol in the form of plates or needles. The yields of the compounds were calculated on the initial 4-phenylthiosemicarbazide derivatives.

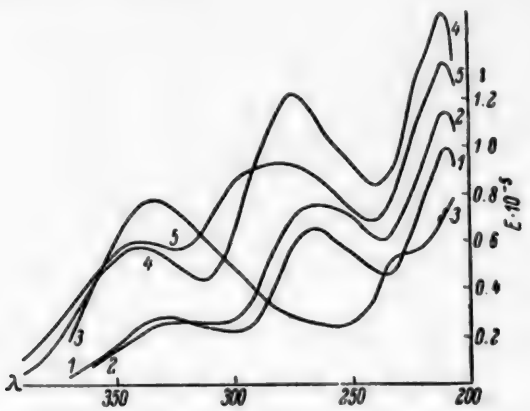
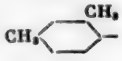
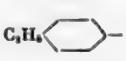
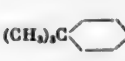
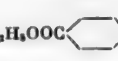
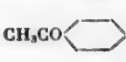
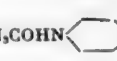
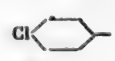
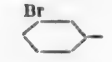
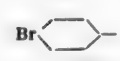
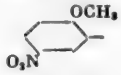
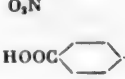
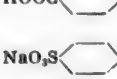
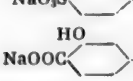
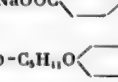
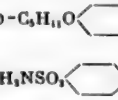
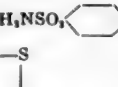
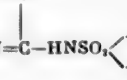


Fig. 1. Ultraviolet absorption spectra of halogen-substituted unsymmetrical derivatives of 1,6-diphenylhydrazodithiodicarbonamide (in alcohol): 1) 1-(m-chlorophenyl)-6-(p-tolyl-hydrazodithiodicarbonamide; 2) 1-(m-chlorophenyl)-6-(p-isoamylhydroxyphenyl)-hydrazodithiodicarbonamide; 3) 1-(m-chlorophenyl)-6-(p-acetophenyl)-hydrazodithiodicarbonamide; 4) 1-(m-chlorophenyl)-6-(p-sulfaminophenyl)-hydrazodithiodicarbonamide; 5) 1-(m-chlorophenyl)-6-(p-carbethoxyphenyl)-hydrazodithiodicarbonamide. Solution concentration for the curves: 1 and 2) $3.3 \cdot 10^{-5}$ M; 3) $6.6 \cdot 10^{-5}$ M; 4) $1.3 \cdot 10^{-5}$ M; 5) $1.65 \cdot 10^{-5}$ M.

Unsymmetrical Halogen-Substituted Derivatives of 1,6-Diphenylhydrazodithiodicarbonamide RNHCSNHNHCSNHR'

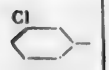
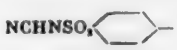
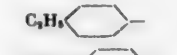
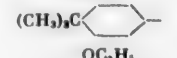
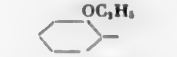
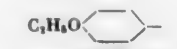
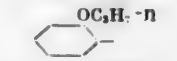
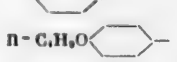
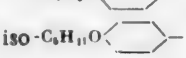
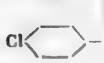
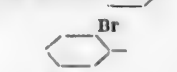
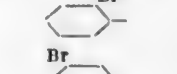
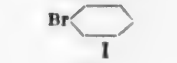
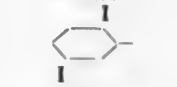
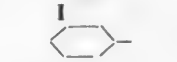
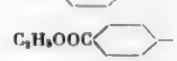
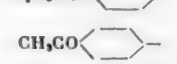
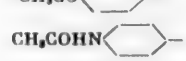
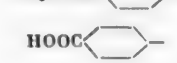
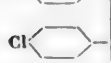
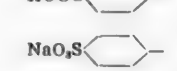
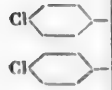
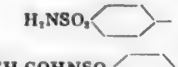
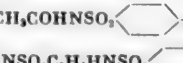
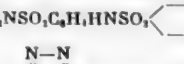
R	R'	Melting point	Yield (%)	Formula	% N found	% N calc.
		167°	80	$C_{15}H_{15}N_4S_2Cl$	15.70, 15.90	15.97
		169	50	$C_{15}H_{15}N_4S_2Cl$	16.02, 16.15	15.97
		145	52	$C_{16}H_{17}N_4S_2Cl$	14.80, 14.96	15.36
		164	55	$C_{16}H_{17}N_4S_2Cl$	15.23, 15.05	15.36
		183	77	$C_{18}H_{21}N_4S_2Cl$	13.92, 13.96	14.27
		does not melt*	98	$C_{17}H_{17}O_2N_4S_2Cl$	14.14, 14.12	13.71
		176	98	$C_{16}H_{15}ON_4S_2Cl$	14.77, 14.72	14.79
		180	91	$C_{16}H_{16}ON_5S_2Cl$	17.55, 17.57	17.79
		168	61	$C_{14}H_{12}N_4S_2Cl_2$	14.78, 14.80	15.09
		170	90	$C_{14}H_{12}N_4S_2ClBr$	13.24, 13.42	13.48
		180	83	$C_{14}H_{12}N_4S_2ClBr$	13.07, 13.18	13.48
		232	95	$C_{15}H_{14}O_3N_5S_2Cl$	17.28, 17.21	17.01
		does not melt*	50	$C_{15}H_{13}O_2N_4S_2Cl$	14.46, 14.52	14.72
		does not melt*	98	$C_{14}H_{12}O_3N_4S_3ClNa$	12.37, 12.43	12.77
		207	95	$C_{15}H_{12}O_3N_4S_2ClNa$	13.30, 13.45	13.39
		170	98	$C_{19}H_{23}ON_4S_2Cl$	12.95, 12.85	13.25
		216	98	$C_{14}H_{14}O_2N_5S_3Cl$	16.72, 16.67	16.84
		176	98	$C_{17}H_{15}O_2N_6S_4Cl$	16.53, 16.62	16.85
		168	91	$C_{16}H_{16}O_3N_5S_3Cl$	14.91, 15.01	15.30
		171	97	$C_{20}H_{19}O_4N_6S_4Cl$	14.58, 14.46	14.72

* > 305°. ** > 300°.

Figs. 1 and 2 give the absorption spectra of unsymmetrical halogen derivatives of 1,6-diphenylhydrazodithiodicarbonamide. The measurements were carried out in alcohol, using an SF-4 spectrophotometer.

EXPERIMENTAL

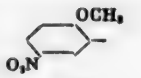
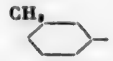
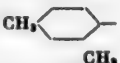
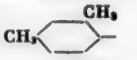
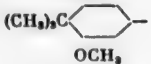
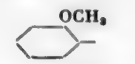
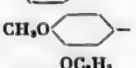
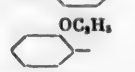
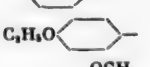
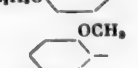
1-(m-Chlorophenyl)-6-(o-tolyl)-hydrazodithiodicarbonamide. A quantity of 4 g of 4-(m-chlorophenyl)-thiosemicarbazide and 3 g of o-tolylisothiocyanate in 25 ml of anhydrous alcohol were placed in a round-bottomed flask

R	R'	Melting point	Yield (%)	Formula	% N found	% N calc.
		250	90	$C_{15}H_{13}O_2N_6S_3Cl$	19.54, 19.49	19.06
		217	50	$C_{15}H_{15}N_4S_2Cl$	16.40, 16.45	15.97
		204	95	$C_{16}H_{17}N_4S_2Cl$	15.03, 15.10	15.37
		201	90	$C_{18}H_{21}N_4S_2Cl$	13.86, 13.88	14.27
		142	45	$C_{16}H_{17}ON_4S_2Cl$	14.55, 14.35	14.72
		160	50	$C_{16}H_{17}ON_4S_2Cl$	14.72, 14.67	14.72
		156	67	$C_{17}H_{19}ON_4S_2Cl$	13.88, 13.90	14.20
		193	63	$C_{18}H_{21}ON_4S_2Cl$	13.26, 13.43	13.71
		173	48	$C_{19}H_{23}ON_4S_2Cl$	13.36, 13.19	13.25
		164	83	$C_{14}H_{12}N_4S_2ClBr$	13.31, 13.34	13.48
		192	83	$C_{14}H_{12}N_4S_2ClBr$	13.10, 13.16	13.48
		204	92	$C_{14}H_{12}N_4S_2ClBr$	13.94, 13.84	13.48
		173	70	$C_{14}H_{12}N_4S_2ClI$	11.63, 11.86	12.11
		173	73	$C_{14}H_{12}N_4S_2ClI$	11.84, 11.62	12.11
		201	64	$C_{14}H_{12}N_4S_2ClI$	11.95, 12.00	12.11
		does not melt *	52	$C_{17}H_{17}O_2N_4S_2Cl$	13.97, 14.03	13.71
		226	90	$C_{16}H_{15}ON_4S_2Cl$	15.14, 15.12	14.79
		163	42	$C_{16}H_{16}ON_5S_2Cl$	18.20, 18.10	17.79
		does not melt*	75	$C_{15}H_{13}O_2N_4S_2Cl$	14.38, 14.46	14.72
		does not melt*	50	$C_{14}H_{12}O_3N_4S_3ClNa$	12.40, 12.20	12.77
		does not melt*	50	$C_{14}H_{14}O_2N_5S_3Cl$	16.54, 16.63	16.84
		183	87	$C_{16}H_{16}O_3N_5S_3Cl$	15.36, 15.40	15.30
		195	91	$C_{20}H_{19}O_4N_6S_4Cl$	14.50, 14.56	14.72
		191	33	$C_{18}H_{18}O_2N_7S_4Cl$	18.78, 18.90	18.58
		230	90	$C_{15}H_{13}O_2N_6S_3Cl$	19.06, 19.22	19.06

* > 300°.

with a reflux condenser. The mixture was boiled for 1 hour on the water bath. After it had cooled, the precipitate was filtered and washed with alcohol. After recrystallization from alcohol the yield of the product was 5.6 g (80%); the m.p. was 167°.

All the unsymmetrical halogen derivatives of 1,6-diphenylhydrazodithiodicarbonamide given in the Table were obtained in a similar way to 1-(m-chlorophenyl)-6-(o-tolyl)-hydrazodithiodicarbonamides.

R	R′	Melting point	Yield (%)	Formula	% N found	% N calc.
Cl		245	86	$C_{15}H_{14}O_3N_5S_2Cl$	16.83, 16.80	17.01
I		182	62	$C_{15}H_{15}N_4S_2I$	12.97, 13.01	12.67
I		169	60	$C_{15}H_{15}N_4S_2I$	13.02, 13.05	12.67
I		211	67	$C_{15}H_{15}N_4S_2I$	12.83, 12.48	12.67
I		184	83	$C_{16}H_{17}N_4S_2I$	12.03, 12.20	12.28
I		182	79	$C_{18}H_{21}N_4S_2I$	11.39, 11.23	11.57
I		180	87	$C_{15}H_{15}ON_4S_2I$	12.52, 12.61	12.23
I		197	81	$C_{15}H_{15}ON_4S_2I$	12.43, 12.31	12.23
I		164	80	$C_{16}H_{17}ON_4S_2I$	11.61, 11.43	11.87
I		169	86	$C_{16}H_{17}ON_4S_2I$	11.92, 11.73	11.87
I		172	88	$C_{15}H_{14}O_3N_5S_2I$	13.51, 13.62	13.92

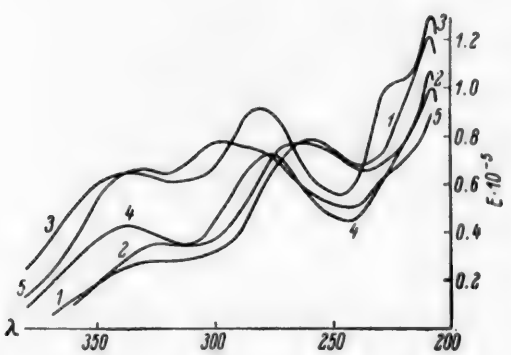


Fig. 2. Ultraviolet absorption spectra of halogen-substituted unsymmetrical derivatives of 1,6-diphenylhydrazodithiodicarbonamide (in alcohol): 1) 1-(p-chlorophenyl)-6-(p-tolyl)-hydrazodithiodicarbonamide; 2) 1-(p-chlorophenyl)-6-(p-isoamylhydroxyphenyl)-hydrazodithiodicarbonamide; 3) 3) 1-(p-chlorophenyl)-6-(p-acetoxyphenyl)hydrazodithiocarbonamide; 4) 1-(p-chlorophenyl)-6-(p-sulfaminophenyl)-hydrazodithiodicarbonamide; 5) 1-(p-chlorophenyl)-6-(p-carbethoxyphenyl)-hydrazodithiocarbonamide. Solution concentration for the curves: 1, 4 and 5) $3.3 \cdot 10^{-5}$ M. 2) $6.6 \cdot 10^{-5}$ M; 3) $1.1 \cdot 10^{-5}$ M.

SUMMARY

56 unsymmetrical halogen derivatives of 1,6-diphenylhydrazodithiodicarbonamide, undescribed in the literature, were synthesized. The ultraviolet absorption spectra of some of the compounds were measured.

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ALKYLATION OF ALKANE SULFONAMIDES

I. ALKYLATION OF ALKANE SULFONAMIDES BY SECONDARY ALCOHOLS

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Original article submitted May 24, 1960

Arenesulfonamides are readily alkylated by secondary alcohols in 80-85% sulfuric acid at 60-70° [1]; during this process, only arenesulfonyl monoalkyl amides (I) are obtained, even with excess secondary alcohol. Dialkyl-substituted amides (II) are not obtained, evidently as a result of the steric hindrances produced when a second alkyl radical is introduced.

$$\underset{\text{(I)}}{ArSO_2NHAlk} \qquad \underset{\text{(II)}}{ArSO_2N(Alk)_2}$$

It was subsequently found that arenesulfonamides are also readily alkylated by tertiary butyl alcohol at low temperature [2]; with an increase in temperature, arenesulfonyl-tertiarybutyl amides are not formed [1]; this is evidently due to the instability of the latter in acid solutions and the readiness with which they decompose into arenesulfonamide and alkene.

With the aim of extending this alkylation reaction of amides of sulfonic acids by secondary alcohols to alkane sulfonamides, we carried out the alkylation of methane sulfonamide and butane-2-sulfonamide with isopropyl and secondary butyl alcohols and cyclohexanol in 80-85% sulfuric acid at 60-70°. It was found that alkane sulfonamides are also readily alkylated by secondary alcohols and cycloalkanols under these conditions, with the formation of monoalkyl-substituted derivatives.

$$RSO_2NH_2 + HOAlk \longrightarrow \underset{\text{(III)}}{RSO_2NHAlk} + H_2O.$$

The alkane sulfonylalkyl amides (III) formed are not extracted from sulfuric acid solution by dichlorethane (in contrast to arenesulfonylalkyl amides); to separate them, the reaction mass was therefore treated with water and extracted with chloroform, which is the most suitable solvent for this purpose. For purification, the alkane sulfonylalkyl amides were crystallized from a mixture of benzene and heptane or were distilled under vacuum. The alkane sulfonylalkyl amides obtained in this way were low-melting crystalline substances or liquids, fairly readily soluble in water. It is noteworthy that methane sulfonylcyclohexylamide is only slightly extracted from a dichlorethane solution by 1.5 N alkali, which indicates a reduction in the acid properties. Liquid alkane sulfonylalkyl amides are not miscible with n-heptane at low temperature.

We also found that benzhydrol readily alkylates alkane sulfonamides in glacial acetic acid in the presence of zinc chloride, with the formation of alkane sulfonic substituted α-aminodiphenyl methane.

$$RSO_2NH_2 + HOCH(C_6H_5)_2 \longrightarrow \underset{\text{(IV)}}{RSO_2NHCH(C_6H_5)_2} + H_2O.$$

α-Alkane sulfaminodiphenyl methanes (IV) are crystalline substances, insoluble in alkali, with distinct melting points; they may be used for the identification of alkane sulfonamides.

EXPERIMENTAL

Methane sulfonamide was prepared by the oxidation of S-methyl isothiourea sulfate [3] in an aqueous solution by chlorine [4] and conversion of methane sulfonyl chloride to the amide by the action of dilute ammonia. Butane sulfonamide was synthesized via butyl thiocyanate and butane sulfonyl chloride [5].

Methane sulfonyl isopropylamide. A quantity of 4.75 g of methyl sulfonamide was dissolved in 20 ml of 80% sulfuric acid and 8 ml of isopropyl alcohol was added in 20 minutes at 60°; the mixture was stirred for 4 hours at 70°. The reaction mass was poured onto 50 g of ice and extracted 3 times with chloroform (50 ml each time). The chloroform layer was dried with anhydrous soda, part of the chloroform was driven off on the water bath and 20 ml of n-heptane was added.

The oil, which came out on cooling, crystallized in the form of colorless plates; the m.p. was 33-36°.

Found %: N 10.10. $C_4H_{11}O_2NS$. Calculated %: N 10.21.

The product dissolved fairly readily in cold water, it was insoluble in cold n-heptane and readily soluble in chloroform.

Methane sulfonyl-sec-butylamide. A quantity of 0.05 g-mole of methane sulfonamide was dissolved in 20 ml of 80% sulfuric acid and 0.1 g-mole of sec-butyl alcohol was added at 50-60°. The mixture was left overnight and was then stirred for 5 hours at 70°, cooled, poured onto 50 g of ice and extracted 3 times with chloroform (50 ml each time). The chloroform extracts (red-brown with an intense green fluorescence) were dried with anhydrous soda and after distillation of the chloroform the residue was distilled under vacuum. It was a colorless mobile liquid with a b.p. of 125-127° (9-10 mm), n_D^{22} 1.4509. It was insoluble in n-heptane in the cold; it dissolved when heated. The yield was 2.4 g (36%).

Found %: N 9.13. $C_5H_{13}O_2NS$. Calculated %: N 9.27.

Methane sulfonyl cyclohexylamide. We dissolved 0.05 g-mole of methane sulfamide in 20 ml of 80% sulfuric acid and added 0.1 g-mole of cyclohexanol at 50-60°; the mixture was stirred for 3 hours at this temperature. The sulfuric acid solution was extracted 3 times with dichlorethane (50 ml each time). The dichlorethane extracts were washed with 1.5 N alkali; by acidification of the alkaline solution we obtained 0.55 g of a substance with an m.p. of 103-105°. After the dichlorethane had been steam distilled, an aqueous solution with a small amount of tar was left in the flask; when the filtered aqueous solution was cooled, colorless elongated prisms were obtained (m.p. 103-105°); the yield was 6.65 g. After the sulfuric acid solution had been diluted with water we obtained a crystalline precipitate, contaminated with tar; after it had been washed with n-heptane and dried, the precipitate had an m.p. of 100-105° (yield 1 g). The total yield was 8.65 g (93%). By crystallization from a mixture of benzene and n-heptane we obtained 5.65 g (64%) of a substance with an m.p. of 105-106.5°.

Found %: N 7.88. $C_7H_{15}O_2NS$. Calculated %: N 7.99.

α-Methane sulfaminodiphenyl methane. A quantity of 4.75 g of methane sulfonamide was dissolved in 25 ml of glacial acetic acid, and 9 g of benzhydrol was added, together with a solution of 5 g of anhydrous zinc chloride in 25 ml of glacial acetic acid. The mass was boiled for 2 hours and was then poured into water. The oil obtained crystallized rapidly; a precipitate came out from the aqueous solution (m.p. 137-145°). The yield was 11.7 g (90%). The precipitate was dissolved in hot methanol with the addition of a small amount of water; a yellowish crystalline precipitate came out on cooling; the m.p. was 144.5-146.5°.

Found %: N 5.01. $C_{14}H_{15}O_2NS$. Calculated %: N 5.36.

It dissolved in concentrated sulfuric acid, the solution having a brick-red color.

Butane-1-sulfonyl isopropylamide. We dissolved 0.02 g-mole of butane-1-sulfonamide in 10 ml of 80% sulfuric acid and 0.05 g-mole of isopropyl alcohol was added at 50-60°; the mixture was stirred for 3 hours at 60-70°; the reaction mass was diluted with water and then extracted twice with dichloroethane (50 ml each time). After the dichlorethane had been distilled, we obtained 1 g of a yellowish oil. When the experiments were repeated with extraction by chloroform, the chloroform layer was separated, the solvent was distilled at atmospheric pressure and the residue was distilled under vacuum. We obtained 2.1 g (59%) of a colorless oil; the b.p. was 172-173° (23-24 mm), n_D^{21} was 1.4507.

Found %: N 7.77. $C_7H_{17}O_2NS$. Calculated %: N 7.81.

Butane 1-sulfonyl sec-butylamide. This compound was synthesized in a similar way to the previous one; after the reaction mass had been diluted with water it was extracted twice with chloroform (50 ml each time), the chloroform layer was washed with 1 N NaOH, the chloroform was driven off and the residue was distilled under vacuum. The b.p. was 174-175° (20 mm). We obtained 2.0 g (52%) of a colorless oil; n_D^{22} was 1.4536.

Found %: N 6.90. $C_8H_{19}O_2NS$. Calculated %: N 7.25.

Butane-1-sulfonyl cyclohexylamide. A quantity of 0.02 g-mole of butane-1-sulfonamide was dissolved in 10 ml of 80% sulfuric acid and 0.05 g-mole of cyclohexanol was added in 30 minutes at 60°; the mixture was then stirred at 60-70° for 4 hours. After the mass had been diluted with water a brown oil separated out. This crystallized after a certain period; the product was crystallized three times from n-octane. We obtained 2 g (46%) of the product in the form of clusters of fine needles (m.p. 71-72°). Butane-1-sulfonyl cyclohexylamide obtained from butane-1-sulfonyl chloride and cyclohexylamine melts at 71.8° [6].

Found %: N 6.24. $C_{10}H_{21}O_2NS$. Calculated %: N 6.44.

α-(Butane-1-sulfamino)-diphenyl methane. We dissolved 0.02 g-mole of butane-1-sulfonamide in 20 ml of glacial acetic acid, and 0.02 g-mole of benzhydrol and 2 g of anhydrous zinc chloride were added. The mass was boiled for 3 hours with a reflux condenser, and it was then diluted with water. The oil which separated out crystallized. The yield was 5.15 g (85%). After crystallization from 75% methanol we obtained 2.33 g of the substance in the form of large crystals; the m.p. was 112-113°.

Found %: N 4.80. $C_{17}H_{21}O_2NS$. Calculated %: N 4.62.

It dissolved in concentrated sulfuric acid, the solution obtained being red.

SUMMARY

1. The alkylation of alkane sulfonamides by secondary alcohols in 80% sulfuric acid was investigated; alkane sulfonylmonoalkyl amides were obtained with good yields by this process.

2. The alkylation of alkane sulfonamides by benzhydrol in glacial acetic acid in the presence of zinc chloride was investigated; alkane sulfonic deriviatives of α-aminodiphenyl methane were obtained by this process.

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REACTIONS OF CARBON SUBOXIDE

IX. REACTION OF ELECTROPHILICALLY SUBSTITUTED AROMATIC AMINES WITH CARBON SUBOXIDE IN AQUEOUS MEDIUM

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The reaction of carbon suboxide with amines was studied mainly in ether solutions until this time. The reaction, in the case of unsubstituted primary amines, went rapidly in the cold and gave quantitative yields of N,N'-substituted malonyldiamides. Electrophilically substituted amines were less reactive. As shown in our previous paper [1] some substituted anilines react with carbon suboxide only upon heating, but with nitroaniline, aminobenzenesulfonic acid, and aminobenzoic acid the reaction generally does not occur.

The literature [2-4] indicates that acetylation of amines by ketene can occur in aqueous solutions. This is because the rate of reaction of ketene with the amine group markedly exceeds the rate with aqueous hydroxyl. It was established that this rule also applies to carbon suboxide: Glycine and carbon suboxide in aqueous solution give a good yield of N,N'-malonyl-bis-glycine [5].

In this connection we decided to study the reaction of carbon suboxide with a series of electrophilically substituted aromatic amines in aqueous medium. In amino acids the acid groups are blocked by salt formation. It was found that the best results are obtained at pH 8.5-9. Carbon suboxide reacts with primary amino groups according to the general scheme:

$$XRNH_2 + C_3O_2 + H_2NRX \longrightarrow XRNHC\overset{\overset{O}{\|}}{C}H_2\overset{\overset{O}{\|}}{C}NHRX.$$
$$X = OH,\ COOH,\ SO_3NH_2.$$

Thus N,N'-malonyl-bis-substituted amines which could not be synthesized with carbon suboxide in nonaqueous media were obtained. Under analogous conditions aniline sulfonic acids (sulfanilic and metanilic acids) with carbon suboxide gave mixtures of unreacted starting materials and unidentified substances. Because of the small amounts and difficult separation of these materials, we were unable to determine their structure. Probably formation of N-malonylanilinesulfonic acid took place. The unique type of behavior of sulfanilic and metanilic acids is explained by the influence of the strongly electronegative sulfonic acid group, which sharply decreases the reactivity of the amine group.

EXPERIMENTAL

Preparation of Carbon Suboxide. Carbon suboxide was obtained by pyrolysis of acetic anhydride solutions of diacetyltartaric anhydride [6]. In the experiments a 150% excess of carbon suboxide, which was diffused into the aqueous amine solution from the pyrolysis furnace, was used.

N,N'-Malonyl-bis-o-aminophenol. Carbon suboxide was passed uniformly through a solution of 1 g of o-aminophenol (m.p. 171-172°) in 35 ml of distilled water. A fine crystalline sediment began to separate immediately. At the end of the reaction, part of the water was removed in vacuo; the residue was filtered by suction, recrystallized from hot methanol, and dried in a vacuum desiccator. M.p. 223-224° (from methanol). Reaction with ferric chloride gave a dark red coloration. Yield 0.9 g (68.5%).

Found %: N 9.9. M 286. $C_{15}H_{14}O_4N_2$. Calculated %: N 9.8. M 286.3.

N,N'-Malonyl-bis-m-aminophenol. m-Aminophenol was obtained by prolonged boiling of an aqueous solution of p-aminosalicylic acid. M.p. 122-123° (purified through the hydrochloride). Carbon suboxide was passed through a

solution of 1 g of m-aminophenol in 40 ml of water. A precipitate appeared at once. Further treatment was as in the previous experiment. M.p. 243-244° (from methanol). Reaction with ferric chloride gave a deep violet coloration. Yield 1.1 g (84%).

Found %: N 9.5. M 288.5. $C_{15}H_{14}O_4N_2$. Calculated %: N 9.8. M 286.3.

N,N'-Malonyl-bis-p-aminophenol. p-Aminophenol melting at 181-182° (with decomposition) (purified through the hydrochloride) was used. A substance melting at 236-238° (from methanol) was prepared in a similar way from carbon suboxide and 1 g of p-aminophenol in 40 ml of water; reaction with ferric chloride was positive. Yield 0.95 g (72.5%).

Found %: N 9.6. M 282. $C_{15}H_{14}O_4N_2$. Calculated %: N 9.8. M 286.3.

All isomeric N,N'-malonyl-bis-aminophenols are readily soluble in methanol and acetone, but poorly soluble in water and ether.

N,N'-Malonyl-bis-o-aminobenzoic acid. Commercial o-aminobenzoic acid with m.p. 142-143° (from water) was used for the reaction. An aqueous (25 ml) solution of 2 g of o-aminobenzoic acid was made alkaline with KOH to pH 9. Then carbon suboxide was passed through the solution; a white fine crystalline sediment soon separated. At the end of the reaction the mixture was concentrated to 1/4 the original volume; the residue was filtered with suction, recrystallized from ethyl acetate, and dried in a vacuum desiccator. M.p. 250-251° (from ethyl acetate). The acid group was determined by titration of a weighed amount with KOH to the phenolphthalein end point. Yield 1.8 g (72%).

Found %: N 8.22; M 345. $C_{17}H_{14}O_6N_2$. Calculated %: N 8.19; M 342.3.

N,N'-malonyl-bis-p-aminobenzoic acid. Commercial p-aminobenzoic acid (m.p. 185-186°, from water) was used for the reaction. p-Aminobenzoic acid (2 g) and carbon suboxide gave a substance melting at 275-277° (with decomposition; from methanol). Yield about 2.2 g (88%).

Found %: N 8.24; M 349. $C_{17}H_{14}O_6N_2$. Calculated %: N 8.19; M 342.3.

N,N'-Malonyl-bis-5-aminosalicylic acid. 5-Aminosalicylic acid decomposing at 261-263° (from methanol) was used. 5-Aminosalicyclic acid (1.5 g) was treated with carbon suboxide as before. At the end of the reaction, the mixture was acidified with hydrochloric acid; the solution was concentrated, and the residue was filtered with suction and recrystallized. M.p. 262-263° (with decomposition; from methanol). Reaction with ferric chloride was positive (dark-green coloration which became violet). Yield 0.6 g (30%).

Found %° N 7.8, M 387. $C_{17}H_{14}O_8N_2$. Calculated %: N 7.5. M 374.4.

N,N'-Malonyl-bis-p-aminosalicylic acid. Commercial p-aminosalicylic acid decomposing at 217-218° was used. p-Aminosalicylic acid (1.5 g) with carbon suboxide gave a substance which melted at 248-249° (from methanol). The ferric chloride reaction was positive (deep-red coloration). The yield was 0.64 g (35%).

Found %: N 7.19. M 385. $C_{17}H_{14}O_8N_2$. Calculated %: N 7.5. M 374.4.

All isomeric N,N'-bis-aminobenzoic and N,N'-bis-aminosalicylic acids were moderately soluble in hot methanol, water, and acetone, but were insoluble in ether.

N,N'-Malonyl-bis-p-aminobenzenesulfonamide. p-Aminobenzenesulfonamide (white streptocide) melting at 163-164° was used. p-Aminobenzenesulfonamide (2 g) was dissolved in 40 ml of water. A precipitate appeared shortly after initial passage of carbon suboxide through the solution. The substance obtained melted with decomposition at 270-271° (from water). The yield was quantitative.

Found %: N 13.66. M 420. $C_{15}H_{16}O_6N_4S_2$. Calculated %: N 13.59. M 412.5.

SUMMARY

1. The reaction between a series of electrophilically substituted anilines and carbon suboxide was studied in aqueous solution.

2. It was shown that since the reaction rate of carbon suboxide is greater with primary amine groups than with aqueous hydroxyl, a series of substituted N,N'-malonyl-bis-anilines could be obtained in satisfactory yields from carbon suboxide in an aqueous medium.

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REACTIONS OF CARBON SUBOXIDE

X. REACTION OF CARBON SUBOXIDE WITH SUBSTITUTED ACYCLIC AMINES

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The reaction of carbon suboxide with esters of α-amino acids in ethereal medium [1] and with glycine, some unsubstituted α-amino acids, and proteins in aqueous medium [2-4] is reported in the literature. These authors established that glycine and glycine ester form N,N'-malonyl-bis-substituted amines with carbon suboxide, but that other α-amino acids and proteins yield substituted malonylmonoamides (or do not react with carbon suboxide at all under the conditions given). There are other data in the literature concerning the reaction of carbon suboxide with substituted aliphatic monoamines. Results of the foregoing studies permit the assumption that during the reaction of α-amino acids with carbon suboxide, leading to the formation of N,N'-malonyl-bis-substituted amines there is a shielding effect by the second substituent on the carbon atom bound for the amine group.

Based on these assumptions, we decided to investigate how the reaction of carbon suboxide with substituted amines is influenced by a methylene barrier between the amino and electrophilic groups. The suggested work to some extent was a continuation of our studies on the reaction of carbon suboxide with substituted alicyclic and aromatic amines in ethereal and aqueous media [5,6].

Malonylation of β-substituted ethylamines by carbon suboxide proceeds in good yields and goes as follows:

$$X{-}CH_2CH_2NH_2 + C_3O_2 + H_2NCH_2CH_2{-}X \longrightarrow X{-}CH_2CH_2NHCOCH_2CONHCH_2CH_2{-}X.$$
$$X = Cl,\ Br,\ OH,\ OC_2H_5,\ COOH.$$

Glycine behaves similarly, according to corresponding data [2]. We were able to isolate only the monosubstituted malonylmonoamide in the case of β-phenyl-β-alanine.

$$C_6H_5CH(CH_2COOH)NH_2 + C_3O_2 \longrightarrow C_6H_5CH(CH_2COOH)NHCOCH{=}C{=}O \xrightarrow{H_2O} C_6H_5CH(CH_2COOH)NHCOCH_2COOH$$

This peculiarity in the behavior of β-phenyl-β-alanine evidently can be explained by the influence of the phenyl radical, which produces steric hindrance and decreased reactivity in the adjacent amine group.

EXPERIMENTAL

Preparation of Carbon Suboxide. Carbon suboxide was obtained by high-temperature pyrolysis of acetic anhydride solutions of diacetyl tartaric anhydride in a quartz tube [7]. Gaseous carbon suboxide was fed directly into the reaction mixture from the pyrolysis furnace. Approximately one 150% excess carbon suboxide was used in the experiments. The yield of carbon suboxide was determined by the anilide method [7].

Reaction of Carbon Suboxide with Glycine. Unlike the previous authors who studied the reaction between carbon suboxide and glycine [2], we used not liquid but gaseous carbon suboxide fed directly into the reaction mixture. Glycine (2 g; m.p. 235-236° with decomposition) was mixed with 15 ml of water and concentrated potassium hydroxide solution added carefully to pH 9. Then a uniform flow of carbon suboxide was passed through the solution, and the mixture was maintained in the pH interval 8.5-9 by the gradual addition of 0.1 N potassium hydroxide through a dropping funnel. At the end of the reaction the mixture was acidified to pH 3 and concentrated in vacuo. The solid residue was leached with hot methanol; the hot solution was filtered from the salt and cooled. The precipitate was substance recrystallized from methanol. It melted at 236-237° (with decomposition, beginning at 225°), which agree with literature data [2]. The yield was 2 g (69%).

Reaction of Carbon Suboxide with β-Chloroethylamine. The hydrochloride of β-chloroethylamine was obtained by a known method [8]. M.p. 141-142° [from alcohol-acetone mixture (1 : 3)]. To 2 g of β-chloroethylamine hydrochloride in 20 ml of water was added two drops of phenolphthalein solution; carbon suboxide was passed through the mixture for one hour. The pH was kept in the interval 8-9 during the reaction process by careful addition of alkali. A fine crystalline residue began to separate at the end of the reaction. At the end of the reaction the mixture was concentrated; the residue was removed by filtration, recrystallized twice from dichloroethane, and dried in a vacuum desiccator. M.p. 140-141° (from dichlorethane). The substance is soluble in methanol and acetone but insoluble in water and ether. The yield was about 2 g (quantitative).

Found %: N 12.26; Cl 30.8. M 231.0. $C_7H_{12}O_2N_2Cl_2$. Calculated %: N 12.33; Cl 31.2. M 227.1.

Reaction of Carbon Suboxide with β-Bromoethylamine. β-Bromoethylamine was obtained by the reaction of β-ethanolamine with hydrobromic acid [9]. M.p. 164°. From 2 g of β-bromoethylamine hydrobromide in 25 ml of water was obtained a substance melting at 122-123°. The yield was 1.4 g (91%).

Found %: N 8.71; Br 51.2. M 310. $C_7H_{12}O_2N_2Br_2$. Calculated %: N 8.86; Br 50.7; M 316.

Reaction of Carbon Suboxide with β-Ethanolamine. Freshly distilled β-ethanolamine boiling at 169-170° was used for the reaction. Carbon suboxide was passed through a solution of 2 g of β-ethanolamine in 10 ml of water for one hour. At the end of the reaction the water was distilled off; the clear oily liquid was fractionated twice in vacuo. It boiled at 174-175° (16 mm). The substance was soluble in water, alcohol, and acetone, but insoluble in ether and benzene. The yield was 2 g (66.8%).

d_4^{20} 1.161, n_D^{20} 1.5021.
Found %: N 14.4. M 197. $C_7H_{14}O_4N_2$. Calculated %: N 14.7. M 190.2.

Reaction of Carbon Suboxide with β-Ethoxyethylamine. β-Ethoxyethylamine was obtained by the reaction of β-chloroethylamine with sodium ethoxide [10]. The reaction was carried out in a sealed tube. An alcoholic solution of sodium ethoxide (6 g of sodium in 100 ml of anhydrous alcohol) and 8 g of β-chloroethylamine hydrochloride were heated for 3 hr at 165° in a sealed tube. At the end of the reaction β-ethoxyethylamine base was liberated from the hydrochloride with potassium hydroxide and dried over barium oxide. The yield was about 4 g (~ 65%). Carbon suboxide was passed through a solution of 2.5 ml of β-ethoxyethylamine in 10 ml of water for 50 minutes. Then the water was distilled off and the clear oily liquid fractionated in vacuo. It boiled at 127-128° (15 mm). The substance dissolved in water and alcohol but was insoluble in ether and benzene. The yield was 1.9 g (72%).

d_4^{20} 1.121, n_D^{20} 1.4921.
Found %: N 11.11. M 244.2. $C_{11}H_{22}O_4N_2$. Calculated %: N 11.37. M 246.3.

Reaction of Carbon Suboxide with β-Alanine. β-Alanine was obtained by a known method [11]. It decomposed at 194-195°. Carbon suboxide was passed through 1 g of β-alanine in 15 ml of water (at pH 9). Then the mixture was acidified and the water distilled off; the substance was recrystallized from methanol and dried several days in a vacuum desiccator. It decomposed at 162-164° (from methanol). The product was soluble in water, poorly soluble in methanol, and insoluble in organic solvents. The yield was 0.8 g (64.5%).

Found %: N 11.57. $C_9H_{14}O_6N_2$. Calculated %: N 11.37.

Reaction of Carbon Suboxide with β-Phenyl-β-alanine. β-Phenyl-β-alanine was obtained by Rodionov's method [12]. It melted at 213-214° (from water). β-Phenyl-β-alanine (1.5 g) in 20 of water was treated as in the previous experiments. The substance obtained was recrystallized three times from benzene. It melted at 109-110° (from benzene). The product was soluble in methanol, acetone, and benzene, poorly soluble in water, and insoluble in ether. The yield was 1.2 g (60%).

Found %: N 5.31. M 259. $C_{12}H_{13}O_5N$. Calculated %: N 5.57. M 251.12.

SUMMARY

1. A study of the reaction between some β-substituted ethylamines and carbon suboxide in aqueous medium showed that N,N'-malonyl-bis-β-substituted ethylamines are formed, as a rule.

2. The syntheses of N,N'-malonyl-bis-β-chloroethylamine, N,N'-malonyl-bis-β-bromoethylamine, N,N'-malonyl-bis-β-ethanolamine and N-malonyl-β-phenyl-β-alanine were not recorded in the literature.

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AROMATIC FLUORINE DERIVATIVES

VII.* PREPARATION OF FLUOROBENZENES

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Polychlorofluorobenzenes have hardly been investigated. A mixture of difluorotetrachlorobenzene and trifluorótrichlorobenzene of undetermined structure was formed in poor yield by the reaction of fluorine and hexachlorobenzene [1]. Pentachlorofluorobenzene was obtained in 4% yield by chlorination of fluorobenzene in the presence of iron. Hexachlorobenzene was the primary reaction product in this case [2]. Pentachlorofluorobenzene can also be obtained in 10% yield by the reaction of potassium fluoride with pentachloronitrobenzene in dimethylformamide [3].

We used the displacement of bromine atoms in bromo fluorobenzenes by chlorine by the action of chlorine in the presence of nuclear chlorination catalysts (better with irradiation of the reaction mass) to prepare polychlorofluorobenzenes. Displacement of bromine in aromatic compounds by chlorine under these conditions was long known. Eibner obtained chlorobenzene by treating bromobenzene with chlorine at room temperature [4]. Miller and Walling [5] studied the displacement of bromine by chlorine in detail, demonstrating the radical character of the reaction. Displacement of bromine in fluorobromoaromatic compounds by chlorine was carried out only with p-fluorobromobenzene, chlorination of which gave p-fluorochlorobenzene in 79% yield [6].

We showed that the bromine atoms in fluorine-containing polybromobenzenes are also easily replaced by chlorine. Fluorine atoms do not undergo this displacement. Thus, pentachlorofluorobenzene was prepared in yields up to 80% by reaction of chlorine with pentabromofluorobenzene in 1,2,4-trichlorobenzene solution at 120-130°.

$$C_6Br_5F \xrightarrow{Cl_2} C_6Cl_5F$$

2,4,5,6-Tetrachloro-1,3-difluorobenzene was obtained in 70% yield by chlorination of 2,4,5,6-tetrabromo-1,3-difluorobenzene. This same compound is formed by the action of chlorine on 2,5-dibromo-4,6-dichloro-1,3-difluorobenzene. In a similar manner 2,4,5-trichlorofluorobenzene was obtained from 2,4-dichloro-5-bromofluorobenzene.

The fluorobromo derivatives are obtained by bromination of the corresponding fluorobenzenes (in the presence of halogenation catalysts). It was shown that fluorobenzene is brominated easily and the bromo derivatives are obtained in good yields. It is interesting to note that monobromo derivatives were not obtained from 4,6-dichloro-1,3-difluorobenzene and 2,4,5-trichlorofluorobenzene. Only dibromo derivatives mixed with starting materials were formed during bromination of these compounds with an insufficiency of bromine. The same thing was observed during the bromination of 1,2,4,5-tetrafluorobenzene [7]. However, these fluorobenzenes formed only mononitro derivatives upon nitration [8].

2,4-Dichloro-5-bromofluorobenzene was obtained in 83% yield by bromination of 2,4-dichlorofluorobenzene. The structure of this product was established by direct synthesis from 2,4-dichloro-5-fluoroaniline.

Pentabromofluorobenzene and 2,4,5,6-tetrabromo-1,3-difluorobenzene were obtained by bromination of fluorobenzene and 1,3-difluoro-4-bromobenzene. From fluorochlorobenzenes we obtained 3,4,5,6-tetrabromo-2-chlorofluorobenzene, 2,4,5,6-tetrabromo-3-chlorofluorobenzene, 2,3,5,6-tetrabromo-4-chlorofluorobenzene, 3,5,6-tri-

*Communication VI, see Zh. ZhOKh 31, 1229 (1961).

bromo-2,4-dichlorofluorobenzene, 2,5-dibromo-4,6-dichloro-1,3-difluorobenzene, 3,6-dibromo-2,4,5-trichlorofluorobenzene, and 2,3,4,5-tetrachloro-6-bromofluorobenzene. The above compounds were not previously described.

Bromination of fluoro- and fluorochlorobenzene derivatives following replacement of bromine by chlorine makes possible preparation of the above polychlorofluorobenzenes in very satisfactory yields.

EXPERIMENTAL

(V. A. Batyakina assisted in the work)

Preparation of 2,4-Dichloro-5-bromofluorobenzene. 1) In a three-necked flask equipped with stirrer, reflux condenser stoppered with a calcium chloride tube, and dropping funnel was placed 3.3 g of 2,4-dichlorofluorobenzene and 0.035 g of iron powder; 1.04 ml of bromine was added through the funnel. The mixture was heated at 50-60° for 3.5 hr, after which it was cooled, treated with ether, and filtered. After evaporation of the ether, 4 g (83%) of 2,4-dichloro-5-bromofluorobenzene in the form of long white needles melting at 63-64° was obtained. After recrystallization from petroleum ether the melting point was 66-66.5°.

Found %: F 8.5. $C_6H_2FCl_2Br$. Calculated %: F 7.8.

The spectrum of a 3% solution in CCl_4 was taken on an IKS-14 spectrophotometer with a sodium chloride prism in the interval 850-1500 cm^{-1}. The band width was 0.01 mm. The absorption peaks found were at 874, 1079, 1125, 1247, 1348, 1452 and 1473 cm^{-1}.

2) To a solution of 5.4 g of 2,4-dichloro-5-fluoroaniline in 50 ml of 15% H_2SO_4 cooled to 0° with mixing was added dropwise a solution of 2.1 g of sodium nitrite in 7 ml of water, after which the mixture was stirred for 30 minutes. The filtered diazo solution was slowly added, with mixing and heating to 40° to a suspension of 15 g of freshly prepared cuprous bromide in 100 ml of water. The mixture was heated at 50° for 10 minutes and allowed to stand overnight. After steam distillation, 2.5 g (37%) of 2,4-dichloro-5-bromofluorobenzene was isolated as white needles melting at 65.5° (from alcohol). A mixed melting point with the product obtained in the foregoing experiment was not depressed. The infrared spectrum was identical to the spectrum of the product obtained in the previous experiment.

Exhaustive Bromination of Fluoro Derivatives. a) Into a three-necked flask equipped with stirrer, reflux condenser stoppered with a calcium chloride tube, and a dropping funnel was charged bromine, and 0.05-0.25 g of alumina was added in small pieces at 0°, after which 30 mmole of the compound being brominated was added through the funnel at a temperature not exceeding 20°. After addition of all reactants the mixture was left at room temperature for 2 hr and then heated at 50-60° for 4 hr, poured onto ice, and filtered. The residue on the filter was washed with a 10% solution of sodium bisulfite (three 100-ml portions), with 10% sodium carbonate (three 150-ml portions), and with water until neutral to litmus. The product was recrystallized from benzene. Compounds 1-6 (table) were obtained in this manner.

b) The compound being brominated (35 mmole) was added in small batches at 0-5° to a mixture of 7 ml of bromine, 7 ml of 60% oleum, and 0.5 g of anhydrous aluminum bromide. The reaction mixture was maintained at 50-60° for 4 hr and poured on ice. Further treatment is given above. Compounds 7-9 (table) were obtained in this manner.

Chlorination of Fluorobromo Derivatives. The reaction was conducted in a quartz Wurtz flask equipped with a thermometer at the bottom and a tube for introducing dry chlorine monohydrate. The flask was warmed by an insulated spiral wrapped around it. The reaction mixture was illuminated by an ultraviolet lamp PRK-4 placed 25 cm from the flask. The reaction was continued until the evolution of bromine stopped.

Preparation of Fluoropentachlorobenzene. Fluoropentabromobenzene (40 g) in 30 ml of 1,2,4-trichlorobenzene was chlorinated at 120-130° for 5-6 hr in a stream of chlorine of 40-50 ml/min. The trichlorobenzene was distilled off, after which the residue was crystallized from methanol. Fluoropentachlorobenzene (16-17.5 g; 73-80%) was obtained as white needles melting at 139-140°. Literature data: m.p., 138° [3], 140° [2].

Found %: F 7.2, 6.7. C_6FCl_5. Calculated %: F 7.1.

Preparation of 2,4,5,6-Tetrachloro-1,3-difluorobenzene. a) 2,4,5,6-Tetrabromo-1,3-difluorobenzene (8 g) was chlorinated at 120-125° for 6 hr (chlorine flow was 20-30 ml/min). By crystallization from methanol we obtained 3.56 g (73%) of 2,4,5,6-tetrachloro-1,3-difluorobenzene melting at 53°. After recrystallization from petroleum ether the long white needles melted at 54°.

Hexahalobenzenes Obtained by Bromination of Fluorobenzene Derivatives

No.	Starting compound	Reaction product	Molar ratio of bromine and starting compound	Yield (in %)	Melting point	Found % F	Empirical formula	Calculated % F
1	Fluorobenzene	Pentabromofluorobenzene	10	97	197°	3.8,3.9	C_6FBr_5	3.3
2	1,3-Difluoro-4-bromobenzene	2,4,5,6-Tetrabromo-1,3-difluorobenzene	6	97	86	8.9,8.6	$C_6F_2Br_4$	8.9
3	o-Fluorochlorobenzene	3,4,5,6-Tetrabromo-2-chlorofluorobenzene	8	94	186	3.9,3.8	C_6FClBr_4	4.3
4	m-Fluorochlorobenzene	2,4,5,6-Tetrabromo-3-chlorofluorobenzene	8	93	175	3.9,4.0	C_6FClBr_4	4.3
5	p-Fluorochlorobenzene	2,3,5,6-Tetrabromo-4-chlorofluorobenzene	8	94	181	4.1,4.2	C_6FClBr_4	4.3
6	2,4-Dichlorofluorobenzene	3,5,6-Tribromo-2,4-dichlorofluorobenzene	6	96	171	4.7,4.9	$C_6FCl_2Br_3$	4.7
7	1,3-Difluoro-4,5-dichlorofluorobenzene	2,5-Dibromo-4,6-dichloro-1,3-difluorobenzene	4	95	67	11.5,11.5	$C_6F_2Cl_2Br_2$	11.1
8	2,4,5-Trichlorofluorobenzene	3,6-Dibromo-2,4,5-trichlorofluorobenzene	4	88	153	5.5,5.8	$C_6FCl_3Br_2$	5.3
9	2,3,4,5-Tetrachlorofluorobenzene	2,3,4,5-Tetrachloro-6-bromofluorobenzene	2	98	145	6.0,5.7	C_6FCl_4Br	6.1

Found %: F 15.2, 15.2. $C_6F_2Cl_4$. Calculated %: F 15.1.

b) By the action of chlorine (20-30 ml/min) on 10 g of 2,5-dibromo-4,6-dichloro-1,3-difluorobenzene at 130-140° for 7 hr we obtained 5.1 g (69%) of a substance melting at 52-53° (from petroleum ether) and containing no bromine. A mixed melting point with the product obtained in the previous experiment was not depressed.

Preparation of 2,4,5-Trichlorofluorofluorobenzene. By chlorination (20-30 ml/min) of 9 g of 2,4-dichloro-5-bromofluorobenzene at 130-140° for 12 hr we obtained 4.9 g (67%) of 2,4,5-trichlorofluorobenzene melting at 61-62° (from methanol). Literature data: m.p. 62° [9]; 64° [10]. A mixed melting point with an authentic sample was not depressed.

SUMMARY

1. A method for obtaining chlorofluorobenzenes by displacement of bromine in bromofluorobenzenes was developed.

2. Fluorobromo- and fluorochlorobromobenzene derivatives were obtained by bromination of fluorobenzene and fluorochlorobenzenes.

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SYNTHESES BASED ON TETRALONE CARBOXYLIC ESTERS

I. PREPARATION OF 3-METHYL- AND 1,3-DIMETHYLTETRALONE-2

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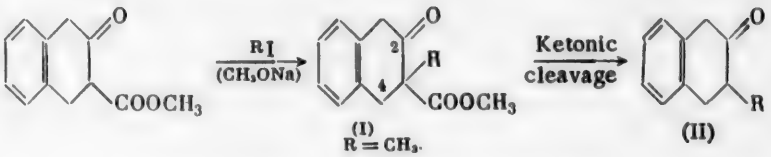
3-Alkyl-substituted 2-tetralones were not obtained before now, which is evidently explained by the early lack of simple synthetic routes to these compounds. A simple method of obtaining 2,3-tetralonecarboxylic acid [1] recently developed in our laboratory provides a method of synthesizing 3-alkyl-substituted 2-tetralones via the ketoester [2] according to the scheme:



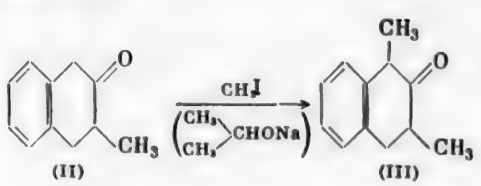
(I) R = CH_3. (II)

This synthesis enabled us to obtain, for example, 3-methyltetralone-2 (II).

Under our conditions for conducting the reaction (addition of sodium methylate at − 10 to − 15° to a mixture of ketoester and methyl iodide, present taken in small excess), the methylation occurs exclusively in the 3-position although the ketoester molecule has other reactive centers (active hydrogen on C-1). This selective alkylation is apparently because the designated conditions are too mild for introducing an alkyl group in the 1-position. These results of our experiment in alkylating unsubstituted β-tetralone have this advantage: This ketone is not methylated under our conditions.

The yield of 3-methyl-2,3-tetralonecarboxylate (I) is 74.4%. Ketonic cleavage leads to the formation of 3-methyltetralone-2 (II) in 62.7% yield.

3-Methyltetralone-2 was converted to 1,3-dimethyltetralone-2 (III) in 80% yield by methylation under more vigorous conditions (Cornforth's method [3]).



(II) (III)

The structure of 3-methyltetralone-2 (II) was established by conversion to 3-methylnaphthol-2 by dehydrogenation with sulfur [4] (29% yield) or with bromine [5] (52% yield). The 2,4-dinitrophenylhydrazone and semicarbazone derivatives of (II) were also obtained.

Dehydrogenation of 1,3-dimethyltetralone-2 (III) gave notably poorer results: Heating with sulfur did not lead to the formation of the corresponding disubstituted β-naphthol, and the yield was only 8.6% 1,3-dimethylnaphthol-2 by dehydrogenation with bromine.

It should be mentioned that methyl 2,3-tetralonecarboxylate is very easily dehydrogenated on heating with sulfur at 200-240°, forming 2,3-naphtholcarboxylic acid in 83.7% yield.

EXPERIMENTAL

Methyl 3-Methyl-2,3-tetralonecarboxylate (I). In a four-necked flask equipped with stirrer reflux condenser, thermometer, and dropping funnel was placed 150 ml of anhydrous methanol, 15 g of methyl 2,3-tetralonecarboxylate and 15.5 g of methyl iodide. Sodium methylate was added (1.68 g of sodium in 30 ml of anhydrous methanol) to the solution over 1 hr at − 15 to − 10°. It was left for 2 hr at − 15° and for 2 hr more at room temperature. The alcohol was evaporated on a water bath and the residual oil taken up in 300 ml of water and extracted three times with 50 ml of ether. The residue after evaporation of the ether (16.49 g) was distilled under vacuum. After two distillations a fraction boiling at 118-120° at 0.5 mm was obtained; n_D^{18} 1.5325. Yield 11.9 g (74.4%).

Found %: C 71.38, 71.21; H 6.78, 6.55. $C_{13}H_{14}O_3$. Calculated %: C 71.54; H 6.47.

2,4-Dinitrophenylhydrazone; orange needles (from alcohol), melting at 233-235°.

Found %: N 13.99, 13.86. $C_{19}H_{16}O_6N_4$. Calculated %: N 14.07.

Semicarbazone: was white needles from alcohol; m.p. 195-196°.

3-Methyltetralone-2 (II). In a round-bottomed flask with reflux condenser 4.65 g of methyl 3-methyl-2,3-tetralonecarboxylate (I) was boiled with 47 ml of 5% potassium hydroxide solution for 1 hr. A slightly yellow oil, which was extracted with ether and dried over sodium sulfate, was steam distilled from the reaction mixture. The residue (3.39 g) after evaporation of the ether was distilled in vacuo. A fraction boiling at 86-87° at 0.5 mm was obtained; $n_D^{18.5}$ 1.5361. Yield 2.39 g (62.7%).

Found %: C 82.02, 81.92; H 7.62, 7.58. $C_{11}H_{12}O$. Calculated %: C 82.36; H 7.55.

Semicarbazone: white platelets (from alcohol); m.p. 184-185°.

Found %: C 66.40, 66.50; H 7.04, 7.06; N 18.31, 18.30. $C_{12}H_{15}ON_3$. Calculated %: C 66.34; H 6.96; N 19.34.

2,4-Dinitrophenylhydrazone: orange needles (from alcohol); m.p. 197-198°.

1,3-Dimethyltetralone-2 (III). In a four-necked flask equipped with stirrer, reflux condenser, thermometer and dropping funnel was dissolved 1.06 g of sodium in 40 ml of anhydrous isopropanol. At room temperature was added 7.37 g of 3-methyltetralone-2, and then with cooling (ice) 9.15 g of methyl iodide in 25 ml of anhydrous isopropanol. After 2 hr heating, the mixture was poured into 300 ml of water and steam distilled; a slightly yellow oil was extracted with ether and dried over sodium sulfate. The oil after evaporation of ether (7.20 g) was distilled under vacuum. A fraction boiling at 100-102° at 1 mm was obtained; $n_D^{17.5}$ 1.5281. Yield 6.39 g (80.0%).

Found %: C 83.26, 83.02; H 8.64, 8.59. $C_{12}H_{14}O$. Calculated %: C 82.72; H 8.10.

Semicarbazone was formed with difficulty, only after two-months standing. The white crystals melted at 175°.

Dehydrogenation of Methyl 2,3-Tetralonecarboxylate (I). In a round-bottomed flask fitted with gas outlet tube was placed 3 g of methyl 2,3-tetralonecarboxylate and 0.47 g of sulfur recrystallized from benzene. The mixture was heated for 4 hr in a metal bath with gradual increase of bath temperature from 200 to 240°. Hydrogen sulfide, volume not determined, was evolved during the reaction. After cooling, the crystallized product was dissolved in 100 ml of ether and extracted four times with 50-ml batches of 5% sodium hydroxide. The alkaline extract was acidified to Congo with 30% sulfuric acid. The yellow precipitate was filtered on a Buchner funnel, washed with water, and dried in a vacuum desiccator. M.p. 216-220°. After precipitation from bicarbonate, the melting point was 224-225°. A mixed melting point with 2,3-naptholcarboxylic acid melted at the same temperature. The yield was 2.31 g (83.7%).

3-Methylnaphthol-2.a) From 2.56 g of 3-methyltetralone-2 (II) and 0.52 g of sulfur under the conditions described above we obtained 0.75 g of a brown-colored substance melting at 153-155°. After recrystallization from carbon tetrachloride the lustrous brown leaflets melted at 157.0-158.7°. Lustrous white leaflets melting at 159.3-160.2° were obtained by vacuum sublimation at 150°. Literature data [6] for 3-methyltetralone-2: m.p. 154-156°, 160.9-161.5°. The yield was 0.75 g (29.1%).

Found %: C 83.45, 83.72; H 6.33, 6.52. $C_{11}H_{10}O$. Calculated %: C 83.51; H 6.37.

Acetyl Derivative: colorless plates (from alcohol); m.p. 65.5−66.4°.

Found%: C 77.87, 77.71; H 6.29, 6.44. $C_{13}H_{12}O_2$. Calculated %: C 77.98; H 6.04.

b) To a solution of 5.06 g of 3-methyltetralone-2 (II) in 40 ml of absolute ether was added a solution of 5.06 g of bromine in 10 ml of absolute ether (with stirring and cooling to 10°) at such a rate that decolorization occurred before addition of the next drop. The ether solution was washed twice with water, with 5% bicarbonate solution, and extracted several times with 5% sodium hydroxide solution. An oil which separated from the alkaline solution upon acidification to Congo red crystallized overnight. The yellow crystals obtained (2.65 g; 52.3%) melted at 120-125°; after three recrystallizations from carbon tetrachloride the melting point was 159.4-160.2°. A mixture with the preparation obtained by sulfur dehydrogenation of 3-methyltetralone-2 did not exhibit melting point depression.

1,3-Dimethylnaphthol-2. From 3.17 g of 1,3-dimethyltetralone-2 and 2.91 g of bromine in 32 ml of absolute ether under the conditions described above (method "b") we obtained 0.27 g (8.6%) of gray fibrous crystals melting at 74-78°. After three recrystallizations from carbon tetrachloride the white needles melted at 88.3-88.9°.

Found %: C 83.59; H 7.05. $C_{12}H_{12}O$. Calculated %: C 83.69; H 7.02.

SUMMARY

1. It was shown that under conditions generally used for alkylation of β-ketoesters, methyl 2,3-tetralonecarboxylate is methylated in the 3-position.

2. The preparation of 3-methyl- and 1,3-dimethyltetralone-2 and their carbonyl-group derivatives is described.

3. The structure of 3-methyl- and 1,3-dimethyltetralone-2 was established by dehydrogenation to the corresponding methylnaphthols.

4. It was established that methyl 2,3-tetralonecarboxylate gives a good yield of 2,3-hydroxynaphthoic acid upon sulfur dehydrogenation.

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INVESTIGATION OF THE MECHANISM FOR THE REACTION OF PHENYLHYDRAZINE WITH NITROSO COMPOUNDS USING N^{15}

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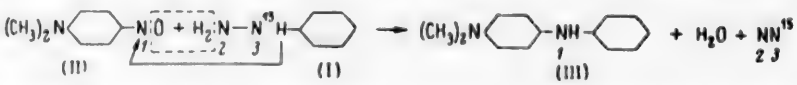
Original article submitted May 20, 1960

Phenylhydrazine (I) usually reacts as a reducing agent, being converted into elementary nitrogen and benzene. This was established experimentally in the case of azobenzene reduction by one of us [1]. During reduction of lead peroxide [2] or potassium hypochlorite [3] azobenzene is partially obtained. The reaction of (I) with diazobenzene is not accompanied by nitrogen evolution, but the intermediate linear tetrazine decomposes by two routes to phenylazide and aniline [4]. Consequently it was of interest of clarify the mechanism of reaction of (I) with nitroso compounds.

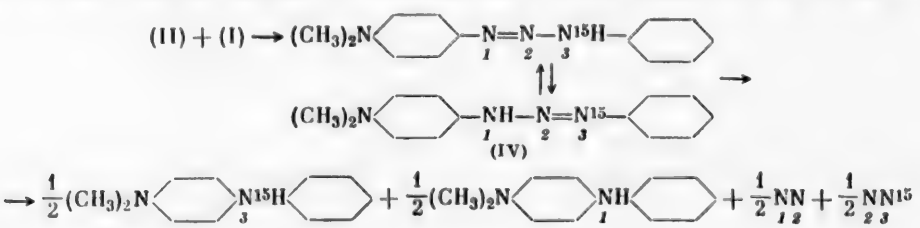
This reaction proceeds by several routes according to the experimental conditions, solvent character, etc. Fischer and Wacker [5] showed that in neutral ethereal solution (I) reacted with p-nitrosodimethylaniline (II) forming p,p'-azoxydimethylaniline. In alcoholic ether solution p-dimethylaminodiphenylamine (III) was formed primarily, with little p,p'azodimethylaniline or N,N-dimethyl-p-phenylenediamine.

The mechanism for the formation of (III) is not clear. Phenylhydrazine can react, as in other examples of reduction, by losing nitrogen and forming (III) with the nitroso group according to the scheme:



(1)

It is possible, however to suppose that condensation occurs first with formation of an intermediate complex or compound with the diazoamino group, analogous to other reactions of nitroso compounds with amines.



(2)

Elimination of nitrogen from the intermediate combination (IV) can occur by two routes owing to active hydrogen on the polynitrogen chain [6,7]. Hydrogen, depending on the substituents on the benzene ring, can to a greater or less extent be localized on one of the external nitrogen atoms or is transferred easily from one to another. Consequently during decomposition of the diazoamino compound, α-nitrogen from (I) must be transferred partly into (III). This can be established with labelled heavy isotopic α-nitrogen in phenylhydrazine.

The reaction between phenylhydrazine containing 9-10% of N^{15} in the α-nitrogen and (II), as well as p-nitrosodiethylaniline (V) was carried out. The isotopic content of nitrogen was determined in the diphenylamine derived. The substances were dissolved in alcohol in stoichiometric amounts and were mixed at room temperature. After the evolution of nitrogen ceased, the derived diphenylamine was extracted with ether and purified. The product was treated by the Kjeldahl procedure, and the ammonia was converted to ammonium chloride. The isotopic content of nitrogen

in the ammonium chloride, determined by mass spectrometry, is given in the table, the data in which show that in the condensation of (V) with (I) the tagged α-nitrogen is not transferred to p-diethylaminodiphenylamine (VI), i.e., it is completely eliminated as elementary nitrogen. During condensation of (II) with (I) a small amount of tagged nitrogen goes into (III). Such a distribution of heavy nitrogen must explain the reaction course according to scheme (1).

Condensation of $C_6H_5N^{15}HNH_2$ with $(CH_3)_2NC_6H_4NO$ and $(C_2H_5)_2NC_6H_4NO$

Expt. No.	Product	Melting point	Initial content of N^{15} in α-N of (I) (in %)	Found N^{15} in N-atoms 1-2	% calc. for 2 N-atom
1	$(CH_3)_2N$(1)—C$_6$H$_4$—NH(2)	127°	9.1	0.62	
1a			9.1	0.65	
2		128	9.1	0.59	
3		126	10.3	0.51	
3a			—	0.47	
4		128	10.3	0.54	
4a		128.5	—	0.57	
				Average 0.56	0.75 *
5	$(C_2H_5)_2N$(1)—C$_6$H$_4$—NH(2)	87	10.3	0.35	
5a			—	0.35	
6		87	10.3	0.35	
6a			—	0.35	
6b			—	0.35	0.37 **

* $2 \cdot 0.56 - 0.37 = 0.75$.

** Original content

These results can correspond to scheme (2) if localization of hydrogen on the 1 N atom in the intermediate triazine (IV) is assumed. Meanwhile, it was shown [8] that of the two possible tautomeric diazoamino compounds.

$$\underset{(a)}{Ar{-}N{=}N{-}NH{-}Ar'} \quad \text{and} \quad \underset{(b)}{Ar{-}NH{-}N{=}N{-}Ar'}$$

from a (a) predominates when Ar has electron-donating or Ar' has electron-accepting substituents (or both together), but form (b) predominates under the opposite conditions. Therefore, in reaction according to scheme (2) the diazoamino compound must be found primarily, i.e., in more than 50% of the cases, in form (VI).

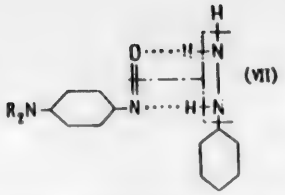
$$R_2N{-}C_6H_4{-}N(1){=}N(2){-}N^{15}(3)H{-}C_6H_5 \quad \text{(VI)}$$

Thus nitrogen NN in (VI) or (III) will be split out, more than $\frac{0.37 + 9.1}{2} = 4.7\%$ N^{15} appearing in the NH group. Consequently, from experiments 5 and 6 [where light (VI) is obtained] scheme (2) is excluded.

In experiments 1-4 with (II) the imino-nitrogen obtained is somewhat heavy. This must deviate due either to contamination or to a secondary process according to scheme (2). Carefully purified material and experimental reproducibility permit the supposition that a secondary process of diazoamino compound formation and its partial decomposition occurs.*

A precisely detailed mechanism according to scheme (1) is not possible without further study. The formation of an intermediate complex (VII) can be postulated by analogy with other reactions of phenylhydrazine [1,9,10].

* On this assumption, fractional reaction according to scheme (2) must be $\frac{0.75 - 0.37}{10.3 - 0.37} \cdot 100 = 4\%$.



(VII)

Further reaction can proceed by radical participation. The variety of products is well explained by combination of the different radicals [11].

Attempts to synthesize diphenylamine derivatives with other nitroso compounds were unsuccessful. The major products in the case of nitrosobenzene, p-nitrosotoluene, and p-nitrosochlorobenzene were the corresponding azoxy compounds. p-Nitrosoacetanilide gave p,p'-azoacetanilide smoothly.

EXPERIMENTAL

α-N^{15}-Phenylhydrazine was obtained from N^{15}-aniline [12] by diazotization with sodium nitrite and subsequent reduction with stannous chloride [13]. From 2 g of aniline with 9.1 or 10.3% of N^{15} was obtained 1.87 g (81%) of phenylhydrazine with n_D^{20} 1.6081.

p-Nitrosodimethylaniline was obtained by the method described in the literature [14] in 95% yield. The melting point of recrystallized product was 85-86° (reported [14] 86.7°).

p-Nitrosodiethylaniline was obtained by a similar method. The crude product was dissolved in ether and precipitated as the hydrochloride by introduction of dry hydrogen chloride. After neutralization with sodium carbonate the precipitated product was recrystallized from alcohol; it melted at 83°. The yield was 97% of theoretical.

Condensation of N^{15}-(I) with (II) was carried out in a neutral alcoholic solution [5]. A solution of 0.3 ml of N^{15}-(I) in 2 ml of alcohol was mixed at room temperature with 0.37 g of (II) dissolved in 7 ml of alcohol. After the evolution of nitrogen ceased, the solution was diluted with 60 ml of water, acidified with 1 ml of concentrated hydrochloric acid, and extracted three times with ether for extraction of acidic and neutral impurities. The acid solution was made basic and extracted three times with ether. The residue after evaporation of the ether was dissolved in 7-8 ml of alcohol and boiled with activated charcoal. The solution filtered from the charcoal was diluted with water and cooled in ice. The residue which appeared was filtered off, distilled in vacuum, and recrystallized from alcohol. The melting point of the p-dimethylaminodiphenylamine obtained was 126-128°; the yield was 10-15% of theoretical.

Condensation of N^{15}-(I) with (V) [15]. A solution of 0.6 g of (V) in 6 ml of alcohol was prepared; to it was added 0.4 g of N^{15}-(I) in 1.5 ml of alcohol. After the reaction the mixture was diluted with 6 ml of water and let stand overnight. Then 3 ml more of water was added; the precipitate formed was filtered off and distilled in vacuum. After one recrystallization from 75% alcohol, p-dimethylaminodiphenylamine melting at 87° was obtained in 25% of theoretical yield.

We thank A. I. Brodski for assistance in this work.

SUMMARY

The reaction between α-N^{15}-phenylhydrazine and p-nitrosodimethyl- and diethylaniline was studied. The reaction goes mainly in the first case and entirely in the second without formation of an intermediate diazoamino compound. In the reaction with p-nitrosodimethylaniline the latter reaction must occur not more than 5% of the time.

The assumed reaction mechanism is discussed.

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THE CONDENSATION OF QUINOLINE-6-ALDEHYDE WITH SOME HETEROCYCLIC COMPOUNDS

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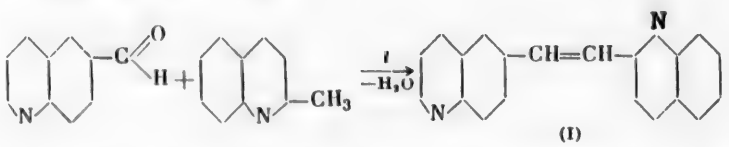
The results of investigations on the reactions of quinoline-6-aldehyde with aromatic amines [1], ketones and esters [2] have been recorded in earlier papers.

In continuation of this work, the condensation of quinoline-6-aldehyde with heterocyclic compounds containing active methyl and methylene groups has been studied.

It is known that some ylidene compounds, in the form of quaternary salts are used in photography [3] and are of interest for the synthesis of acetylenic compounds with heterocyclic radicals [4].

When quinoline-6-aldehyde reacts with quinaldine, 2-(quinol-6-ylrinyl)-quinoline (I) is formed. The experiments were carried out at various reaction temperatures (145-175°) and with various times of heating the reactants. The yield of the base (I) ranged from 30 to 61%.



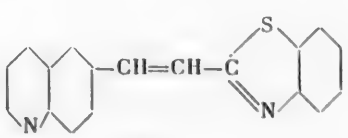
(I)

Condensation of the aldehyde with lepidine does not take place even on heating to 260-265°. However, in the presence of zinc chloride as acid catalyst, a vigorous reaction takes place at 195-200°. No pure 4-(quinol-6-ylvinyl)-quinoline could be isolated from this reaction.

According to results of Izmail'skii and Solodkov [5], the condensation of benzaldehyde and lepidine also leads to the formation of a complex mixture of products. They synthesized 4-styrylquinoline in good yield by the reaction of benzylideneaniline with lepidine.

The reaction of quinoline-6-aldehyde with 2-methylbenzthiazole proceeds with the formation of 2-(quinol-6-ylvinyl)-benzthiazole (II) (at 230–240°, yield 43%) and with 2-methyl-[1,2]-naphthothiazole with the separation of 2-(quinol-6-ylvinyl)-[1,2]-naphthothiazole (III) (at 255 – 260°, yield 26%).

The reaction of the aldehyde with 2-methyl-5-phenylbenzoxazole proceeds at a higher temperature (285 – 290°). Under these conditions, 2-(quinol-6-ylvinyl)-5-phenylbenzoxazole (IV) was obtained in a yield of 19.5%,



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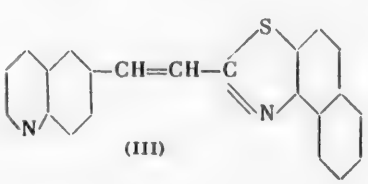

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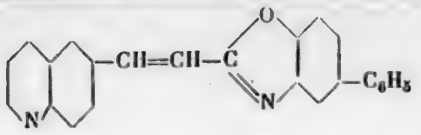

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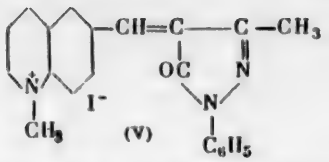

(V)

The condensation of quinoline-6-aldehyde with an active methylene group of a heterocyclic base was carried out with 1-phenyl-3-methylpyrazol-5-one. On heating the reactants at 155 – 160°, the formation of a mixture of products took place; no pure quinol-6-ylmethylene-1-phenyl-3-methylpyrazole-5-one could be isolated from this. The latter was identified in the form of the monomethiodide (V) (yield 57%).

A. E. Porai-Koshits has shown the difficulty of obtaining individual arylmethylene-1-phenyl-3-methylpyrazolones in consequence of the occurrence of side reactions with the formation of bis-(pyrazolon-4-yl)-arylmethane compounds [6]. Obviously analogous reactions take place during the condensation of quinoline-6-aldehyde.

The condensation products obtained (II-IV), on reaction with methyliodide, gave quaternary salts of the quinol-6-yl radical, but mono- and dimethiodides were synthesized only in the case of the base (I).

EXPERIMENTAL PART

2-(quinol-6-ylvinyl)-quinoline (I). A mixture of 3 g of the aldehyde (b.p. 75 – 76°) and 2.8 g of quinoldine was heated for 1 hour in a metal bath at 165 – 175°.* After recrystallization from alcohol (5 ml), 2.63 of pale yellow crystals with m.p. 146 – 147° were obtained. A further 0.59 g of crystals with m.p. 148° was isolated from the mother liquor. The total yield was 3.22 g (59.7%). On repeated crystallization, almost colorless crystals with m.p. 148° were obtained.

The substance dissolves on heating in ether and alcohol and dissolves readily in chloroform, glacial acetic acid, and benzene; it does not dissolve in water.

Found %: N 9.72. $C_{20}H_{14}N_2$. Calculated %: N 9.92.

On heating the reactants for 1 hour at 165 – 175° in the presence of anhydrous zinc chloride (20%), a mixture of products was obtained from which only 33.4% of the base (I) was isolated.

In experiments at temperatures of 165 – 175° (2 hours), 145 – 155° (1 hour), and 145 – 155° (2 hours), 30.0, 38.9, and 61.4%, respectively, of the base (I) were obtained.

Monomethiodide. A mixture of 0.2 g of the substance in 4 ml of anhydrous methanol and 0.5 ml of methyl iodide was boiled for 4 hours. A yield of 0.23 g (76.7%) of golden yellow crystals with m.p. 225-226° (from alcohol) was obtained.

The substance is sparingly soluble on heating in methyl and ethyl alcohols and in glacial acetic acid; it is soluble in water.

Found %: I 29.61. $C_{21}H_{17}N_2I$. Calculated %: I 29.92.

When the reactants were allowed to stand for one month, 74.7% of the monomethiodide, with m.p. 225 – 226° (mixed melting point) was obtained.

On heating the methiodide of quinoline-6-aldehyde [1] with quinaldine in solution in glacial acetic acid and acetic anhydride, a resinous product was obtained.

Dimethiodide. A mixture of 0.2 g of the substance in 5 ml of glacial acetic acid and 0.5 ml of methyl iodide was boiled for 6 hours. A yield of 0.3 g (75%) of dark orange crystals with m.p. 274-276°** (after 2-fold washing with hot glacial acetic acid) was obtained.

The substance is very sparingly soluble on heating in anhydrous alcohol and glacial acetic acid; it is soluble in water.

Found %: I 45.51. $C_{22}H_{20}N_2I_2$. Calculated %: I 44.84.

2-(quinol-6-ylvinyl)-benzthiazole (II). A mixture of 3 g of the aldehyde and 2.9 g of 2-methylbenzthiazole was heated at 235 – 240° for 1 hour. After recrystallization from alcohol (5 ml), 2.35 g of reddish orange crystals with m.p. 167 – 167.5° were obtained. After repeated crystallization, pale orange crystals with m.p. 169-170° were obtained.

* Here and in subsequent experiments the temperature of the metal bath is given.

** The melting point was determined (as in all the subsequent experiments) by immersing a capillary in a bath heated to 200°.

The substance dissolves on heating in alcohol, acetone, chloroform, benzene, with difficulty in ether, and readily in glacial acetic acid; it is insoluble in water.

Found %: N 9.42. $C_{18}H_{12}N_2S$. Calculated %: N 9.72.

Monomethiodide. A mixture of 0.3 g of the substance in 10 ml of anhydrous methyl alcohol and 0.5 ml of methyl iodide was boiled for 6 hours. A yield of 0.32 g (72.7%) of dark yellow crystals with m.p. 273 – 276° (from glacial acetic acid) was obtained.

The substance is sparingly soluble on heating in methyl and ethyl alcohols and glacial acetic acid; it dissolves in water.

Found %: I 29.79. $C_{19}H_{15}N_2SI$. Calculated %: I 29.50.

On heating the reactants in glacial acetic acid for 10 hours, the monomethiodide (73.3%), with m.p. 274 – – 275° (after two washings with hot glacial acetic acid), was again obtained.

2-(Quinol-6-ylvinyl)-[1,2]-naphthothiazole (III). A mixture of 1.5 g of the aldehyde and 1.9 g of 2-methyl-[1, 2]-naphthothiazole was heated at 225 – 260° (the flask was immersed in the bath previously heated to 200°) for 2 hours. After recrystallization from alcohol (3 ml), 0.83 g of pale brown crystals with m.p. 199 – 200° were obtained. On crystallization from glacial acetic acid they formed greenish yellow microcrystals, m.p. 203°.

The substance dissolves on heating in alcohol, acetone, benzene, glacial acetic acid, readily in chloroform, and sparingly in ether; it is insoluble in water.

Found %: N 8.42. $C_{22}H_{14}N_2S$. Calculated %: N 8.30.

Monomethiodide. A mixture of 0.2 g of the substance in 20 ml of benzene and 0.5 ml of methyl iodide was boiled for 5 hours. A yield of 0.17 g (60.7%) of dark yellow crystals with m.p. 257 – 258° (after two washings with hot glacial acetic acid) was obtained.

The substance is very sparingly soluble on heating in benzene, anhydrous alcohol, and glacial acetic acid; it is soluble in water.

Found %: I 26.23. $C_{23}H_{17}N_2SI$. Calculated %: I 26.48.

On heating the reactants in glacial acetic acid for 25 hours, the monomethiodide, m.p. 256–258° (after two washings with hot glacial acetic acid) (mixed melting point), was again obtained.

2-(Quinol-6-ylvinyl)-5-phenylbenzoxazole (IV). A mixture of 1.06 g of the aldehyde and 1.42 g of 2-methyl-5-phenylbenzoxazole was heated at 285–290° (the flask was immersed in the bath previously heated to 280°) for 45 min. After recrystallization from alcohol (4 ml), 0.46 g of pale brown crystals with m.p. 172° were obtained. On crystallization from benzene with activated carbon they formed colorless crystals, m.p. 178°.

The substance is sparingly soluble on heating in alcohol and ether, readily soluble in acetone, chloroform, and benzene, and insoluble in water.

Found %: N 7.73. $C_{24}H_{16}ON_2$. Calculated %: N 8.04.

Monomethiodide. A mixture of 0.18 g of the substance in 10 ml of benzene and 0.5 ml of methyl iodide was boiled for 3 hours. A yield of 0.15 g (60.0%) of dark yellow crystals with m.p. 263–264° (after washing with hot glacial acetic acid) was obtained.

The substance is very sparingly soluble in hot benzene, alcohol, and glacial acetic acid, and is soluble in water.

Found %: I 26.26. $C_{25}H_{19}ON_2I$. Calculated %: I 25.89.

4-(Quinol-6-ylmethylene)-1-phenyl-3-methylpyrazol-5-one. A mixture of 1.9 g of the aldehyde and 2.1 g of 1-phenyl-3-methylpyrazolone was heated at 155–160° for 15 min. (until the evolution of water ceased). After crystallization from alcohol (4 ml) 2.13 g of reddish orange crystals with m.p. 148–149° were obtained. Subsequent crystallizations failed to give a substance with a constant melting point.

Monomethiodide (V). A mixture of 0.15 g of the substance (m.p. 148–149°) in 5 ml of glacial acetic acid and 0.4 ml of methyl iodide was boiled for 3 hours. A yield of 0.12 g (57.1%) of wine-red crystals with m.p. 243–244° (from glacial acetic acid) was obtained.

The substance dissolves with difficulty in hot alcohol, glacial acetic acid, and water.

Found %: I 27.78. $C_{21}H_{19}ON_2I$. Calculated %: I 27.88.

SUMMARY

1. The condensation of quinoline-6-aldehyde with quinaldine, lepidine, 2-methylbenzthiazole, 2-methyl-[1, 2]-naphthothiazole, 2-methyl-5-phenylbenzoxazole, and 1-phenyl-3-methylpyrazole-5-one has been studied.

2. 2-(Quinol-6-ylvinyl)-quinoline, 2-(quinol-6-ylvinyl)-benzthiazole, 2-(quinol-6-ylvinyl)-[1,2]-naphthothiazole, and 2-(quinol-6-ylvinyl)-5-phenylbenzoxazole have been synthesized. 4-(Quinol-6-ylmethylene)-1-phenyl-3-methylpyrazole-5-one has been synthesized in the form of its monomethiodide.

3. The monomethiodides of all the condensation products and the dimethiodide of 2-(quinol-6-ylvinyl)-quinoline have been obtained.

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THE SYNTHESIS OF ESTERS AND OTHER DERIVATIVES OF CARBOXYLIC ACIDS UNDER CONDITIONS OF ACID CATALYSIS FROM CARBON MONOXIDE, OLEFINS, AND ACYLATABLE COMPOUNDS

VI. SYNTHESIS OF ESTERS FROM $C_8 - C_{10}$ α-OLEFINS OF NORMAL STRUCTURE

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We have previously [1] reported on the new synthesis of esters of carboxylic acids from olefins, carbon monoxide, and alcohols, in the presence of concentrated sulfuric acid as catalyst, that we have developed. By this method, we obtained methyl and ethyl esters from $C_4 - C_7$ olefins in a yield of 60–70% of the initial olefin and 70–100% of the carbon monoxide absorbed [2], and also from C_5–C_6 cycloolefins of more complex structure (dihydrocyclopentadiene) [3].

In the present work, we studied the formation of methyl and ethyl esters from oct-1-ene, and dec-1-ene by the same method. The first stage of the reaction, the interaction of the olefin, CO and H_2SO_4 was carried out in a stainless steel autoclave with a turbomixer (800 rev/min), and a dropping funnel for the liquid olefin at 20–40° and an initial pressure of CO of 80 atm; in the second stage, the methyl or ethyl alcohol was added to the reaction mixture. The yield of esters was 70–85% on the initial olefin.

Esters of the following acids were obtained as the main reaction products: from oct-1-ene, α,α-dimethylheptanoic (60–70% in the mixture of esters); from non-1-ene, α,α-dimethyloctanic (55–71%); and from dec-1-ene, α,α-dimethylnonanoic (57–78%).

On the basis of the results obtained in the present work and previously [2], it may be concluded that the method of synthesis of esters developed may be used as a preparative method for obtaining α,α-dimethylalkanoic acids and their esters from carbon monoxide, alcohols, and the appropriate olefin having one atom of carbon less than the acid.

EXPERIMENTAL

The initial olefins used in the investigation were obtained from alcohols by converting them into acetates with acetic anhydride and acetyl chloride and decomposing the acetates at 460–490° over glass wool in a current of nitrogen [4]. The olefins thus obtained, after appropriate purification, were distilled through a column. Non-1-ene (b.p. 145.5–146.8°, n_D^{20} 1.4160, d_4^{20} 0.7300, bromine number 126.5, content of unsaturated material 99.5%) and dec-1-ene (b.p. 170.9-171.2°, n_D^{20} 1.4215, d_4^{20} 0.7408, bromine number 113.3, content of unsaturated material 99.0%) were synthesized from primary monyl alcohol (b.p. 213-219°, n_D^{20} 1.4351, d_4^{20} 0.8293) and primary decyl alcohol (b.p. 223-226°, n_D^{20} 1.4368, d_4^{20} 0.8294), respectively. Oct-1-ene (b.p. 121.2-122.1°, n_D^{20} 1.4091, d_4^{20} 0.7153, bromine number 140.2, content of unsaturated material 98%) was isolated by fractional distillation in a column with an efficiency of 90 theoretical plates from a mixture of octenes obtained by the same method from secondary octyl alcohol (b.p. 177-178°, n_D^{20} 1.4240, d_4^{20} 0.8189).

Literature data [5] for octene; b.p. 121.28°, n_D^{20} 1.4087, d_4^{20} 0.7149; for non-1-ene: b.p. 146.87°, n_D^{20} 1.4157, d_4^{20} 0.7292; for dec-1-ene: b.p. 170.57°, n_D^{20} 1.4215, d_4^{20} 0.7408.

The method of carrying out the synthesis has been described earlier [2,3]. The esters obtained were fractionated and the anilides were prepared from the fractions corresponding to the individual esters and recrystallized from alcohol to constant melting point. The separate fractions of the individual esters were saponified by boiling for 10-12

TABLE 1. Synthesis of Esters from $C_8 - C_{10}$ α-olefins

Expt. No.	Amount in ml			Pressure of CO (in atm)		Absorption of CO		Yield of esters		
	H_2SO_4	olefin	alcohol	initial	final	liters	% of theoretical	in ml	in % of CO absorbed	in % of initial olefin
1	500	Oct-1-ene 70	Methyl 150	70	46	7.1	70	70	100	79.5
2	500	Oct-1-ene 70	Ethyl 150	70	46	7.1	70	68	100	71.0
3	500	Non-1-ene 165	Methyl 150	80	52	16.5	77	175	89.0	81.5
4	500	Non-1-ene 165	Ethyl 150	80	52	16.5	77	185	100	85.0
5	500	Dec-1-ene 170	Methyl 150	90	17	21.5	100	160	100	78.2
6	500	Dec-1-ene 170	Ethyl 150	90	17	21.5	100	185	78.2	84.8

TABLE 2. Esters Obtained from $C_8 - C_{10}$ α-olefins

Initial olefin	Acid from which ester derived	Content (in % by in the mixture of esters)	Boiling range (pressure in mm)	d_4^{20}	n_D^{20}	Melting point of the anilide
		Methyl				
Oct-1-ene	α,α-Dimethylheptanoic	60.0	188.1—189.1°	0.8756	1.4203	92°
Non-1-ene	α,α-dimethyl-octanoic	71.4	51—53 (3)	0.8751	1.4252	77
Dec-1-ene	α,α-dimethyl-nonanoic	78.3	68—70 (3)	0.8729	1.4287	91.5
		Ethyl				
Oct-1-ene	α,α-dimethylheptanoic	70.0	50—53 (3)	0.8622	1.4190	92
Non-1-ene	α,α-dimethyl-octanoic	55.1	59—62 (3)	0.8632	1.4232	77
Dec-1-ene	α,α-dimethyl-nonanoic	57.5	71—74 (3)	0.8629	1.4271	91.5

hours with a 20% alcoholic solution of KOH. The solutions of the potassium salts of the carboxylic acids were treated with a 30% solution of sulfuric acid; the separated carboxylic acids were dissolved in hexane and dried with anhydrous sodium sulfate. After the hexane had been distilled off, the acids were distilled off, the acids were distilled in vacuo from a Favorskii flask. The anilides and amides were prepared from the carboxylic acids obtained. On determining the melting point of a mixture of the anilides obtained from the methyl and ethyl esters of the same acid or of mixtures of each of these anilides with the anilides prepared directly from this acid, no depression of the melting point was observed.

The conditions of carrying out the experiments on the synthesis of esters and their results are given in Table 1; the content and constants of the fractions corresponding to the individual esters are given in Table 2; the constants of the carboxylic acids obtained by saponification of the individual esters are given in Table 3. For comparison, Table 3 includes acids obtained by the saponification of esters synthesized by us earlier [2,3]. As can be seen from the results given, oct-1-ene, non-1-ene and dec-1-ene give methyl and ethyl esters with a yield of 71-85% on the initial olefin. The bulk of the ester mixtures obtained consisted of esters of α,α-dimethylalkanoic acids having 1 carbon atom more than the initial olefin; no individual esters of isomeric or higher-molecular-weight acids could be isolated in sufficient amounts for analysis. From oct-1-ene, a mixture of esters containing 60-70% of the ester of α,α-dimethylheptanoic acid was obtained. The mixture obtained from non-1-ene contained 55-71% of the ester of α,α-

TABLE 3. Acids Obtained by Saponification of the Individual Esters

Name of the acid	Boiling point (pressure in mm)		d_4^{20}		n_D^{20}		Melting point of the anilide		Melting point of the amide	
	found	according to literature data	found	according to literature data	found	according to literature data	found	according to literature data	found	according to literature data
α,α-dimethylbutyric	186—186.5°	184—187° [7]	0.9273	—	1.4143	1.4142 [9]	92.0	90.5—91° [7]	102	101.5—102° [7]
α,α-dimethylvaleric	104 (13)	101—102 [8] (11)	0.9183	—	1.4215	1.4208 [9]	74	73.5 [10]	96	95—96 [8]
α,α-dimethylhexanoic	114—116 (11)	119—122 [7] (13)	0.9145	—	1.4280	—	88	88 [7]	92	92—92.5 [7]
α,α-dimethylheptanoic	125—125.5 (12)	145—145.6 [6] (32)	0.9080	—	1.4321	1.4298 [9]	92	91.5—92 [7]	101	101.5—102 [6]
α,α-dimethyloctanoic	139—141 (12)	139—141.5 [7] (13)	0.9035	—	1.4358	—	77	66.5—67 [7]	102	102.5—103 [7]
α,α-dimethylnonanoic	148—149 (12)	139—148 [9] (20)	0.9001	—	1.4392	1.4363—1.4390 [9]	91.5	—	—	—

dimethyloctanoic acid. In addition to these, α,α-dimethyloctanoic acid itself (b.p. 103-104° at 3 mm, n_D^{20} 1.4358, d_4^{20} 0.9033) was isolated from these mixtures by distillation in an amount of 21.4% by volume from the methyl ester mixture and 33.6% from the ethyl ester mixture. Dec-1-ene yielded mixtures of esters containing 58-78% by volume of the appropriate ester of α,α-dimethylnonanoic acid. In addition to the esters, fractions were also obtained from the mixtures which corresponded to dimethylnonanoic acid itself (b.p. 111-112° at 3 mm, n_D^{20} 1.4398, d_4^{20} 0.0947 in amounts of 15.8 and 40.0% by volume from the methyl ester mixtures and the ethyl ester mixtures, respectively. According to data in the literature: the methyl ester of α,α-dimethylheptanoic acid has b.p. 79-80° at 17 mm, n_D^{25} 1.4182-1.4189; the anilide of this acid has m.p. 91.5-92° [6]. The anilide of α,α-dimethyloctanoic acid has m.p. 66.5-67° [7]. By saponification of the separate esters, α,α-dimethylheptanoic, α,α-dimethyloctanoic and α,α-dimethylnonanoic acids were obtained. α,α-Dimethylbutyric, α,α-dimethylvaleric, and α,α-dimethylhexanoic acids were also obtained from the esters synthesized earlier. The physical constants of all the acids obtained and the melting points of their derivatives (anilides and amides) agree with the data in the literature (Table 3).

SUMMARY

1. Syntheses have been achieved of esters of carboxylic acids from $C_8 - C_{10}$ olefins, carbon monoxide, and methyl or ethyl alcohol at 20-40° and a pressure of 80 atm. of CO in the presence of concentrated sulfuric acid as catalyst. The yield of esters was 80-100% on the carbon monoxide absorbed and 70-85% on the initial olefin.

2. Methyl and ethyl esters of the following acids were obtained as the main reaction products: from oct-1-ene, α,α-dimethylheptanoic; from non-1-ene, α,α-dimethyloctanoic; from dec-1-ene, α,α-dimethylnonanoic.

3. The method of synthesizing esters developed may be used as a preparative method for carboxylic acids containing a quaternary carbon atom in the α position and their esters.

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A NEW METHOD OF SYNTHESIS OF ESTERS OF PHOSPHONIC AND THIOPHOSPHONIC ACIDS

XXXV. THE ADDITION OF PHOSPHORUS PENTACHLORIDE TO DIENE HYDROCARBONS AND OF PARTIAL ESTERS OF ACIDS OF PHOSPHORUS TO BUTADIENYLPHOSPHONIC ESTERS

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The addition of phosphorus pentachloride to divinyl was first reported by Kosolapoff [1]. The acid chlorides were not isolated by him but were worked up in alcoholic alkali. On the basis of the mixture of products obtained, boiling over a wide temperature range, Kosolapoff concluded that 1,2- and 1,4-addition took place in the first instance. K. N. Anisimov and N. E. Kolobova [2,3] isolated formic acid on heating the ozonides of the chlorides of chlorobutenylphosphonic and chloromethylbutenylphosphonic acids with hydrogen peroxide. This lead them to the conclusion that the addition of phosphorus pentachloride to divinyl took place in the 1,2-position and that its addition to isoprene occurred in the unsubstituted vinyl group. There is more recent patent information on the addition of phosphorus pentachloride to divinyl in the 1,2-position [4].

From the results we have obtained on the addition of phosphorus pentachloride to divinyl and isoprene, we have come to conclusions which differ from those of the previous investigators.

On oxidizing the chloride of the chlorobutenylphosphonic acid (I) obtained as the sole reaction product from phosphorus pentachloride and divinyl with potassium permanganate, chloroacetic acid was isolated and identified*. The infrared spectrum of (I) has a double-bond frequency at 1660 cm^{-1}, a frequency at 3028 cm^{-1} corresponding to the stretching vibrations of =CH−, and an intense absorption band at 969 cm^{-1} which is characteristic for the trans-CH = CH-grouping.

The interaction of 1,4-dichlorobut-2-ene with triethyl phosphite yielded the diethyl ester of 4-chlorobut-2-enylphosphonic acid, oxidation of which with potassium permanganate gave chloroacetic acid. Consequently, no allyl rearrangement took place during the reaction. The constants of this ester and the ester obtained by esterification of (I) (b.p. 121-122° at 1.5 mm, n_D^{20} 1.4670, d_4^{20} 1.1483), are identical.

$$ClCH_2{-}CH{=}CH{-}CH_2Cl \xrightarrow{P(OC_2H_5)_3} ClCH_2{-}CH{=}CH{-}CH_2{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2$$

$$ClCH_2{-}CH{=}CH{-}CH_2\overset{\overset{O}{\|}}{P}Cl_2 \xrightarrow{2C_2H_5OH}$$

(I)

It may be concluded from these results that phosphorus pentachloride adds to divinyl in the 1,4-position according to the equation:

$$CH_2{=}CH{-}CH{=}CH_2 + 2PCl_5 \longrightarrow CH_2Cl{-}CH{=}CH{-}CH_2PCl_4 \cdot PCl_5 \xrightarrow{2SO_2}$$

$$\longrightarrow ClCH_2{-}CH{=}CH{-}CH_2\overset{\overset{O}{/}}{P}Cl_2 + POCl_3 + 2SOCl_2.$$

(I)

* Chloroacetic acid is also formed when the reaction mixture is oxidized before its distillation.

However, the presence in the infrared spectrum of (I) of very weak absorption bands with frequencies of 996 and 902 cm^{-1}, which are characteristic for the $CH_2 = CH -$ group, is probably due to the presence of the 1,2 addition product as an impurity.

Esters of Butenediyldiphosphonic and – Thiophosphonic Acids

Substituent				Yield (in %)	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D		Content of phosphorus in %		Content of double-bonds (in %)*
R	R′	R″	X					found	calc.	found	calc.	
CH_3	CH_3O	H	O	60	175—176° (1.5)	1.4663	1.1981	69.36	69.64	20.41	20.66	83
C_2H_5	C_2H_5O	H	O	73	181—182 (2)**	1.4585	1.1287	79.30	78.88	19.08	18.90	92
n-C_3H_7	n-C_3H_7O	H	O	63	186—187 (1.5)	1.4580	1.0973	88.57	88.12	17.41	17.41	89
C_2H_5	C_2H_5O	H	S	50	184 (1.5)	1.4809	1.1320	86.46	86.37	17.73	18.02	95
C_2H_5	C_6H_5	H	O	70	219 (3.5)	1.5105	1.1572	93.00	92.63	17.02	17.22	83
CH_3	CH_3O	CH_3	O	60	213—214.5 (10)	1.4660	1.1662	74.40	74.26	19.68	19.74	88
C_2H_5	C_2H_5O	CH_3	O	77	216—218 (10)	1.4604	1.1161	83.95	83.50	17.92	18.12	94
n-C_3H_7	n-C_3H_7O	CH_3	O	63	189—190 (1)	1.4580	1.0864	93.01	92.73	16.76	16.76	90
C_2H_5	C_2H_5O	CH_3	S	57	216—217 (10.5)	1.4801	1.1212	90.69	90.98	17.08	17.32	93
C_2H_5	C_6H_5	CH_3	O	77	199—200 (1)	1.5110	1.1481	97.61	97.24	16.57	16.57	80

* The double bond determination was carried out by the method of Mc Ilhinney.

** Substance (V).

On oxidizing the chloride of 2-chloro-2-methylbut-3-enyl phosphonic acid (II) with potassium permanganate, formic acid was obtained. The infrared spectrum of (II) exhibits absorption bands at 1003 and 927 cm^{-1} which are characteristic for out-of-plane deformation vibrations of the carbon – hydrogen bonds of an unsubstituted vinyl group. The slight increase in these frequencies as compared with the normal values may be explained by the presence of substituting groups in the radical on the α-carbon atom [5]. It follows from the results obtained that phosphorus pentachloride adds to isoprene mainly on the substituted vinyl group with the formation of the product (II).

(II)

This conclusion is in harmony with the electronic polarization of isoprene usually assumed for addition reactions and the diene synthesis and agrees with the data which exist on the addition of halogen-containing reactants to it [6,7].

We showed earlier that diethyl phosphite adds to the diethyl ester of butadienylphosphonic in the presence of sodium ethoxide [8]. The position of the double bond in the addition product was not established. In the present investigation, we carried out the addition of dimethyl-, diethyl-, and di-n-propyl phosphites, diethyl thiophosphites and ethyl hydrogen phenylphosphonate to the diethyl esters of butadienyl- and methylbutadienylphosphonic acids. In contrast to the data of [2,3], the synthesis of the latter substances was carried out in one stage by the action of alcohol and an excess of triethylamine on the appropriate acid chloride. The addition reaction proceeds extremely vigorously in the presence of sodium ethoxide with a considerable heat effect. The addition yielded the esters of butenediyldiphosphonic and butenediyldithiophosphonic acids in yields of 60-70%. The characteristics of the addition products are given in the Table. The presence of a double bond in them was confirmed by bromination by Mc Ilhinney's method.

On the addition of partial esters of acids of phosphorus to butadienylphosphonic ester, 1,2- 3,4- and 1,4-addition products may possibly be formed, according to its mode of polarization. In the case of the addition of diethylphosphite, they will have the structures (III, IV, V).

Infrared absorption spectra. 1) chloride of 4-chlorobut-2-enylphosphonic acid (I); 2) chloride of 2-chloro-2-methylbut-3-enylphosphonic acid (II); 3) diethyl ester of allylphosphonic acid (VI); 4) diethyl ester of prop-1-enylphosphonic acid (VII); 5) diethyl ester of but-2-enylphosphonic acid (VIII); 6) tetraethyl ester of but-2-ene-1,4-diyldiphosphonic acid (IX); 7) addition product of diethylphosphite to the diethyl ester of butadienylphosphonic acid (V); 8) addition product of diethylphosphite to the diethyl ester of methylbutadienylphosphonic acid.

The position of the double bond was established from a comparison of the infrared absorption spectrum of the addition product with the spectra of a series of model compounds (see Figure). The following were chose as model compounds: the diethyl ester of allylphosphonic acid (VI), the diethyl ester of prop-1-enylphosphonic acid (VII), and the diethyl ester of but-2-enylphosphonic acid (VII), and the diethyl ester of but-2-enylphosphonic acid (VIII).

$CH_2=CH-CH_2-P(=O)(OC_2H_5)_2$ (VI)

$CH_3-CH=CH-P(=O)(OC_2H_5)_2$ (VII)

$CH_3-CH=CH-CH_2P(=O)(OC_2H_5)_2$ (VIII)

In the spectrum of (VI) there are a double-bond frequency of 1641 cm^{-1} and frequencies of 1422 and 3090 cm^{-1} connected with planar deformation and stretching vibrations characteristic for an unsubstituted vinyl group. In the spectrum of (VII) the intensity of the 1634 cm^{-1} frequency rises, which may be explained by the conjugation of the carbon – carbon double bond with the P = O group: the 3090 cm^{-1} frequency is absent, and a very weak frequency of 3020 cm^{-1}, characteristic for a – CH = group, appears. In the spectrum of (VIII), there is no absorption band in the region 1660-1630 cm^{-1}, which is explained by a diminution in the intensity of the double-bond absorption band with the displacement of the double bond from the end of the chain to the center of the molecule. The spectrum has the frequency of 3027 cm^{-1} which is characteristic for a – CH = CH – group.

The product of the addition of diethyl phosphite to butadienylphosphonic ester has an infrared spectrum fundamentally similar to the spectrum of compound (VIII) and differing from the spectra of compounds (VI) and (VII).

In order to demonstrate the structure of the addition compound conclusively, the tetraethyl ester of but-2-ene-1,4-diyldiphosphonic acid (IX) was synthesized from 1,4-dibromobut-2-ene and triethyl phosphite by an Arbuzov rearrangement.

The constants of (IX) agree completely with the constants of the addition product. The infrared spectra of (IX) and the addition product also proved to be identical.

From the results obtained we came to the conclusion that the addition product has the structure (V), and consequently, the addition of diethylphosphite acid to butadienylphosphonic ester is in the 1,4-position. The infrared spectrum of the addition product of diethylphosphite to the diethyl ester of methylbutadienylphosphonic acid also resembles the spectra of (VIII) and (IX) and differs from the spectra of (VI) and (VII). Evidently, the addition of partial esters of acids of phosphorus to methylbutadienylphosphonic ester takes place in the 1,4-position.

EXPERIMENTAL PART

Synthesis of the chloride of 4-chlorobut-2-enylphosphonic acid (I). In a three-necked flask with a stirrer and a reflux condenser were placed 500 g of phosphorous pentachloride and 600 ml of dry benzene, and, with ice-water cooling, divinyl was added until the increase in weight was 90-100 g. Next day, the crystalline addition product was treated with sulfur dioxide until it was completely transformed into the liquid state. After distilling off the benzene, phosphoryl chloride and thionyl chloride, the residue was distilled in vacuum with a Widmer column. After repeated distillation, 4.5 g of a fraction boiling in the range 110-142° (12 mm) and 220 g of the chloride of 4-chlorobut-2-enylphosphonic acid (88% yield) with b.p. 142-143° (12 mm), n_D^{20} 1.5210, d_4^{20} 1.4440 were obtained. Literature data for the acid chloride are [2]: b.p. 103-105° (2 mm), n_D^{20} 1.5200, d_4^{20} 1.4452 [2].

Oxidation of the chloride of 4-chlorobut-2-enylphosphonic acid. To 15.5 g of the acid chloride in 1 liter of water, 31.8 g of powdered potassium permanganate dioxide was filtered off and treated with hot water. The filtrate was evaporated to 100 ml, acidified with dilute sulfuric acid and repeatedly extracted with ether. After the ether had been distilled off, 2.5 g of crystalline chloroacetic acid, having m.p. 61-62° after recrystallization, was isolated. A mixed sample with material melted at 62°.

Synthesis of the chloride of 2-chloro-2-methylbut-3-enylphosphonic acid. To 360 g of phosphorus pentachloride in 500 ml of dry benzene, 65 g of isoprene was added dropwise with stirring and cooling. On the next day, the crystalline addition product was treated with sulfur dioxide in order to convert it to the liquid state. After the benzene, phosphoryl chloride and thionyl chloride had been distilled off, the residue was repeatedly distilled in vacuo. Three grams of a fraction boiling in the range 110-145° (10 mm) and 170 g of the chloride of 2-chloro-2-methylbut-3-enylphosphonic acid (90% yield) with m.p. 146-148° (12 mm), n_D^{20} 1.5240, d_4^{20} 1.3910 were obtained. Literature data for the acid chloride are [3]: b.p. 107-108° (2 mm), n_D^{20} 1.5230, d_4^{20} 1.3910.

Oxidation of the chloride of 2-chloro-2-methylbut-3-enylphosphonic acid. Twenty grams of the acid chloride in 1 liter of water was oxidized with 38 g of potassium permanganate. Next day, the manganese dioxide was filtered off. The filtrate was acidified with dilute sulfuric acid and extracted with ether. After the ether had been distilled off, formic acid with b.p. 100°, n_D^{20} 1.3715 was isolated. Literature data [9]: b.p. 100.7°, n_D^{20} 1.3714. The qualitative calomel reaction for formic acid gave a positive result.

Synthesis of esters of butadienylphosphonic acids. In a flask with a mixer, a reflux condenser, and a dropping funnel were placed 33 g of anhydrous alcohol, 50 g of triethylamine, and 150 ml of absolute ether. The mixture was cooled with snow and stirred while 29 g of the chloride of 4-chlorobut-2-enylphosphonic acid (I) in 50 ml of ether was added. The reaction mixture was allowed to stand overnight. The triethylamine hydrochloride was filtered off, the ether was distilled off, and the residue was distilled in vacuo. A yield of 15 g of the diethyl ester of buta-1,3-dienylphosphonic acid with b.p. 122-123° (13 mm), n_D^{20} 1.4749, d_4^{20} 1.0451 was obtained.

The diethyl ester of 2-methylbuta-1,3-dienylphosphonic acid with b.p. 92-93° (1 mm), n_D^{20} 1.4768, d_4^{20} 1.0410 was obtained in a similar manner.

The constants of the compounds obtained agreed with the data in the literature [2,3].

Reaction of 1,4-dichlorobut-2-ene with triethyl phosphite. A mixture of 15.5 g of dichlorobut-2-ene and 10 g of triethyl phosphite was heated under a reflux condenser for 18 hours at 130-140°. After vacuum distillation, 8 g of the diethyl ester of 4-chlorobut-2-enylphosphonic acid was obtained.

B.p. 123° (2 mm), n_D^{20} 1.4670, d_4^{20} 1.1485, MR_D 54.76; calc. 54.41.
Found %: P 13.56, 13.45. $C_8H_{16}O_3PCl$. Calculated %: P 13.68.

Oxidation of the diethyl ester of 4-chlorobut-2-enylphosphonic acid. Oxidation of 9.5 g of the ester in 800 ml of water was carried out with 21.6 g of potassium permanganate at 5-10°, as described above. Chloroacetic acid (1.5 g) with m.p. 61-61.5° was isolated.

Addition of partial esters of acids of phosphorus to esters of butadienyl- and methylbutadienylphosphonic acids. The reaction was carried out with equimolecular amounts of the unsaturated ester and the dialkylphosphites, and diethylthiophosphite, and also ethyl hydrogen phenylphosphonate, and in the presence of sodium ethoxide. The reactions were extremely vigorous, with a large evolution of heat; the reaction flasks were cooled with water. After the addition of the ethoxide, the reaction mixtures were heated for 30 min on the boiling water bath and distilled in vacuo.

Reaction of 1,4-dibromobut-2-ene with triethyl phosphite. A mixture of 10.7 g of 1,4-dibromobut-2-ene and 17 g of triethyl phosphite was heated under a reflux condenser for 25 hours at 140-160°. After distillation in vacuo, 11.5 g of the tetraethyl ester of but-2-ene-1,4-diylphosphonic acid (IX) was obtained. B.p. 181-182° (2 mm), n_D^{20} 1.4595, d_4^{20} 1.1287.

The infrared spectra were taken on a double-beam spectrophotometer (of the firm of Hilger) with an NaCl prism in a film, and on an IKS-14 with an LiF prism in a film.*

The diethyl ester of allylphosphonic acid (VI) was obtained by the reaction of allyl bromide with sodium diethyl phosphite [10]. b.p. 92-93.5° (10 mm), n_D^{20} 1.4348.

The diethyl ester of prop-1-enylphosphonic acid (VII) was obtained from 1,2-dibromopropane and triethyl phosphite [11]. B.p. 78-80° (2.5 mm), n_D^{20} 1.4325.

The diethyl ester of but-2-enylphosphonic acid (VIII) was obtained by the reaction of 1-chlorobut-2-ene with sodium diethyl phosphite [10]. B.p. 112° (12 mm), n_D^{20} 1.4385.

SUMMARY

1. It has been shown that phosphorus pentachloride adds to divinyl to form the acid chloride of 4-chlorobut-2-enylphosphonic acid, and to isoprene to form the acid chloride of 2-chloro-2-methylbut-3-enephosphonic acid.

2. The addition of partial esters of acids of phosphorus to butadienylphosphonic and methylbutadienyl phosphonic esters takes place at the 1,4-positions with the formation of esters of but-2-ene-1,4-diyldiphosphonic acids.

* The spectra were taken by E. G. Yakova, to whom the authors express their grateful thanks.

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THE IONOGENIC ADDITION OF HALOGENS TO BIS-METHYLENE BASES OF NITROGEN HETEROCYCLES

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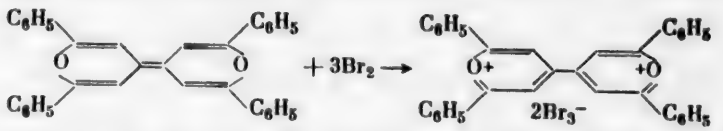
Original article submitted May 30, 1960

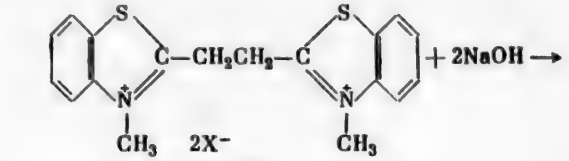
In 1924, Arndt et al. [1] observed a peculiar reaction between tetraphenylbi-4-pyranylidene and bromide:



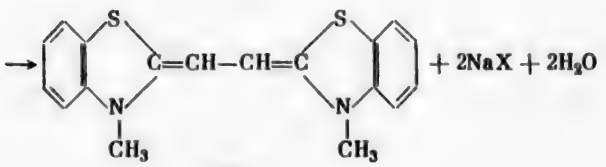
The reaction goes in such a way that two atoms of bromine are reduced to bromine anions and the tetraphenylbipyranylidene takes up two positive charges with a simultaneous rearrangement of the bonds. The product was a dipyrilium salt which was isolated in the form the hexabromide. The reaction is reminiscent of the action of bromine on a divalent metal. Bixanthenylidene reacts with bromine in an analogous fashion.

Some years later, similar reactions of the ionogenic addition of halogens were described by Wizinger [2] and Madelung [3], who investigated the action of halogens on derivatives of tetraarylethylenes containing dimethylamino, amino, or methoxy groups in the para positions of the aryl residues.

We decided to study the ionogenic addition of halogens to unsaturated compounds of more complex structure, namely two bis-methylene bases of benzthiazole. We obtained the simplest of them (II) by the action of alkali on an aqueous solution of the bis-(dimethyl sulphate) derivative of di-(benzthiazolyl)-ethane (I, X = CH_3SO_4), according to the equation:



(I)

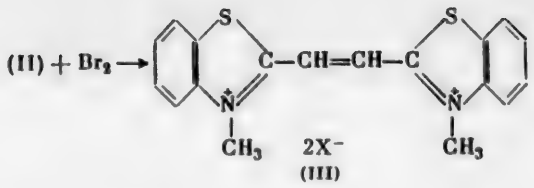


(II)

Substance (II) consists of yellow needles with m.p. 245-246°.* The unpurified base decomposed on storage in the course of a few days. The pure compound may be stored in a sealed tube indefinitely.

As we had assumed, the base (II) adds on halogens in exactly the same way as the tetra-substituted ethylenes of Arndt, Wizinger, and Madelung. If bromine is added to a solution of (II) in chloroform, the mixture at first darkens, but after that, as one mole of bromine is added, it again becomes clear, and the chloroform-insoluble orange salt (III) (X = Br) separates as a precipitate in almost quantitative yield.

*All melting points are corrected.



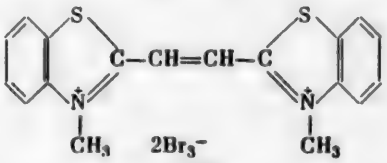
(III)

Any excess of bromine added does not react.

Under the same conditions, we obtained from the base (II) a yellow dichloride and a crimson-red dithiocyanate. The action of iodine led to an insoluble brown addition product, apparently a hexaiodide. These salts, apart from the hexaiodide, are readily soluble in water and alcohol and are insoluble in non-polar solvents. The dichloride and dibromide crystallize from water in the form of dihydrates. By the action of sodium perchlorate on aqueous solutions of the dichloride or the dibromide, we obtained the diperchlorate, which did not contain water of crystallization.

In contrast to the dibromides of tetraarylethylenes [2], the dibromide (III) did not liberate bromine on heating. The hexaiodide, on heating in vacuo above 200°, liberated iodine, but did not give the initial base.

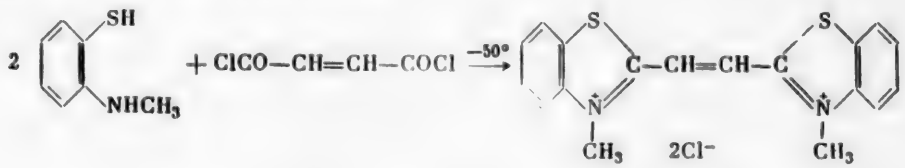
It was observed than an aqueous solution of the dibromide (III) was capable of adding a further two molecules of bromine, forming a microcrystalline orange precipitate. The absorption curve of the product obtained coincides almost precisely with the absorption curve of the initial dibromide; consequently, no addition of bromine to the double bond takes place, and the product must be assigned the structure of the hexabromide (IV).



(IV)

On boiling an aqueous solution of the hexabromide, it liberates bromine and is reconverted into the dibromide.

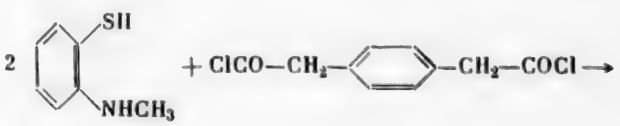
We confirmed the structure of the unsaturated chloride (III, X = Cl) through its alternative synthesis by condensing o-methylaminothiophenol with the dichloride of fumaric acid. This condensation was reported by A. I. Kiprianov and Z. N. Pazenko [4]; however, we had to alter the reaction conditions somewhat. The product of interest to us was obtained only on cooling with dry ice and acetone.

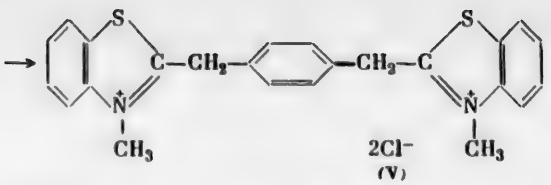


It proved to be identical with the product of the action of chlorine on the bis-methylene base (II).

Fig. 1 shows the absorption curves for the di-(methyl chloride) derivative of di-(benzothiazolyl)-ethane (I, X = Cl) and the di-(methyl bromide) derivative of di-(benzothiazolyl)-ethylene (III, X = Br) in aqueous solutions and of the bis-methylene base (II) in alcoholic solution.

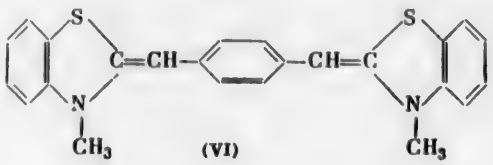
The second bis-methylene base that we investigated was obtained in the following way. By the condensation of of the dichloride of p-phenylenediacetic acid with o-methylaminothiophenol, we synthesized the di(methyl chloride) derivative of ω,ω'-bis-(benzothiazol-2-yl)-p-xylene (V).





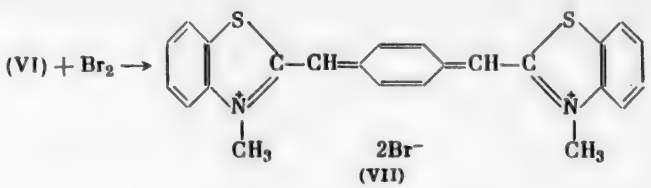
(V)

By the action of alkali on an aqueous solution of the salt (V), we obtained the bis-methylene base (VI).



(VI)

If one mole of bromine is allowed to act on a solution of the base (VI) in chloroform, a yellow-orange microcrystalline precipitate with m.p. 216-217° (with decomposition) separates. The product is soluble in water acidified with hydrobromic acid. All the bromine contained in this salt is precipitated by silver nitrate. On the addition of sodium perchlorate to a solution of the dibromide, the yellow diperchlorate precipitates. All this shows that the bromine has added by an ionogenic mechanism.



(VII)

The salt (VII), in spite of the presence of a quinonoid ring in its molecule, is completely stable – apparently because of the presence of a chain of conjugated double bonds. The stability of a quinonoid ring included in a conju-

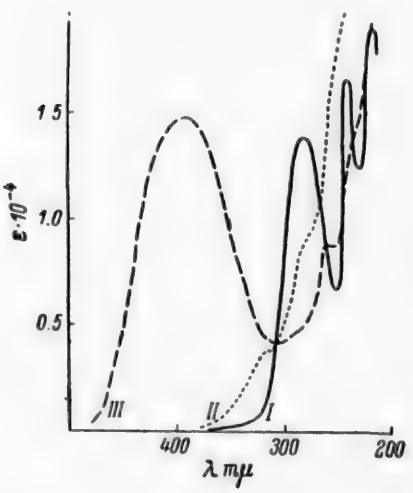


Fig. 1.

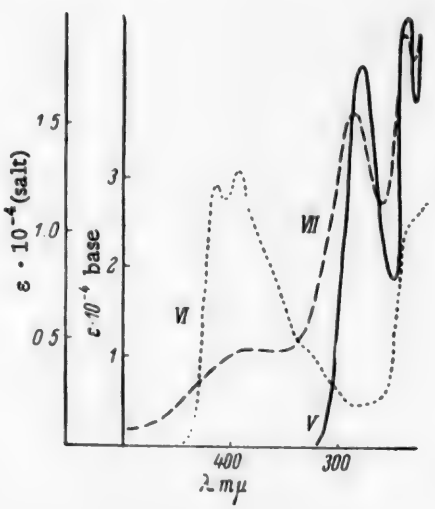


Fig. 2.

gated chain appears in the reaction of an aqueous solution of the salt (VII) with bromine. Here, as in the case of the salt(III), it adds on two molecules of bromine and forms a hexabromide, which readily liberated bromine on heating in water. This compound may also be obtained by the direct action of three moles of bromine on the bis-methylene base (VI) in chloroform. Judging from the similarity of the absorption curves of the hexabromide and the dibromide (VII), the structure of the cation of the salt does not change on reaction with bromine.

Figure 2 gives the absorption curves of the di-(methyl chloride) derivative (V) and the di-(methyl bromide) derivative (VII) in aqueous solutions and of the bis-methylene base (VI) in alcohol.

EXPERIMENTAL PART

1,2-Di-(benzothiazol-2'-yl)-ethane. A mixture of 9 g of succinic acid and 20.3 g of o-aminothiophenol was boiled in a flask with a fractionating column and an upright condenser for 1.5 hours. Water was distilled off amounting to 5.2 ml (by calculation, 5.5 should be distilled off). After cooling, the product was ground with a 10% solution of caustic soda and washed with water. The yield of crude di-(benzothiazolyl)-ethane was 21.2 g (94%); after crystallization from 200 ml of alcohol with active carbon, it was 14 g (62%) of a product with m.p. 134-136° (m.p. 137° [5]).

The bis-(dimethyl sulphate) derivative was obtained by heating the base with four moles of dimethyl sulphate in xylene at 130° for 5 min. The quaternary salt was washed with ether and recrystallized from alcohol. A yield of 76% of greenish crystals with m.p. 220-222° (with decomposition) was obtained.

The di-(methyl bromide) derivative (I, X = Br) was obtained by the action of potassium bromide on a concentrated aqueous solution of the bis-(dimethyl sulphate) derivative. After crystallization from water, it formed orange plates with m.p. 296-297° (with decomposition).

Found %: Br 30.54, 30.70; H_2O 7.10. $C_{18}H_{18}N_2S_2Br_2 \cdot 2H_2O$. Calculated %: Br 30.65; H_2O 6.80.

The di-(methyl chloride) derivative (I, X = Cl) was obtained similarly to the di-(methyl bromide) derivative. It formed orange needles (from 50% alcohol) with m.p. 278° (m.p. 288° with decomposition [5], 285-286° [4]).

Found %: Cl 16.03, 16.00; H_2O 8.95. $C_{18}H_{18}N_2S_2Cl_2 \cdot 2H_2O$. Calculated %: Cl 16.36; H_2O 8.31.

1,2-bis-(3'-methylbenzothiazol-2'-ylidene)-ethane (II). On stirring 6.3 g of the bis-(dimethyl sulphate) derivative of 1,2-di-(benzothiazolyl)-ethane with 30 ml of water, about half the substance went into solution. Then, with continued stirring, 6.3 g of caustic soda in 16 ml of water was added. The yellow precipitate was separated, washed several times with water, and dried in vacuo over P_2O_5. The yield was 3.72 g (100%). After crystallization from benzene, 1.62 g of yellow needle-like crystals with m.p. 245-246° were obtained. The melting point did not change when the substance was sublimed in vacuo at 200°.

Found %: N 8.59, 8.60; S 19.99, 19.92. $C_{18}H_{16}N_2S_2$. Calculated %: N 8.65; S 19.75.

Di-(methyl chloride) derivative of 1,2-di-(benzothiazol-2'-yl)-ethylene (III, X = Cl).

a) To a solution of 0.87 g of the bis-methylene base (II) in 40 ml of chloroform, a 2% solution of chlorine in carbon tetrachloride was added dropwise with stirring. At first a dark-colored precipitate was formed which, on further addition of chlorine, became bright yellow. The precipitate was separated and washed with chloroform. The yield of unpurified product was 0.97 g (97%). The yellow filtrate after evaporation gave a small amount of an orange mass. Purification of the substance was carried out by dissolving it in methanol and precipitating it with benzene. A yield of 0.39 g (40%) of a yellow microcrystalline powder with a decomposition temperature of 263-265° was obtained.

Found %: Cl (Carius microdetermination), 15.71, 15.99; (Volhard titration), 15.72. $C_{18}H_{16}N_2S_2Cl_2 \cdot 2H_2O$. Calculated %: Cl 16.44.

b) In accordance with the information given in [4], a toluene solution of 2.45 g of fumaroyl chloride was run into a solution of 4.45 g of o-methylaminothiophenol in toluene with stirring and cooling with ice and salt. The pale yellow precipitate formed was separated off, washed with benzene and ether, and twice recrystallized from aqueous alcohol with active carbon. A yield of 1.7 g of crystals with m.p. 278° (according to [4], the m.p. is above 300°). The substance proved to be the di-(methyl chloride) derivative not of di-(benzothiazolyl)-ethylene but of di-(benzothiazolyl)-ethane (I, X = Cl). It gave no depression of the melting point with the di-(methyl chloride) derivative of di-(benzothiazolyl)-ethane and showed an identical absorption curve in aqueous solution.

The experiment was repeated in chloroform solution, cooled with a mixture of acetone and solid carbon dioxide. On mixing solutions of 5.35 g of o-methylaminothiophenol and 2.95 g of fumaroyl chloride, a red color appeared which rapidly faded. On warming to room temperature, a copious precipitate was formed which became orange at 40°. The chloroform was distilled off, the residue dissolved in 40 ml of methanol, and cooled to -50°. Orange crystals separated. They were filtered off and washed with cooled methanol. The yield was 1.81 g (45%), m.p. 268-269°. Judging from a mixed melting point and from the coincidence of the absorption curves in aqueous solution, the product is the di-(methyl chloride) derivative of 1,2-di-(benzothiazolyl)-ethylene (III, X = Cl).

Found %: Cl 16.65. $C_{18}H_{16}N_2S_2Cl_2 \cdot 2H_2O$. Calculated %: Cl 16.45.

The di-(methyl bromide) derivative of 1,2-di-(benzothiazol-2'-yl)-ethylene (III, X = Br) was obtained from (II) and bromine in chloroform similarly to the preceeding salt. After two crystallizations from water with active carbon, it formed large orange needles with m.p. 291-293°.

Found %: Br 30.62, 30.72; H_2O 7.4. $C_{18}H_{16}N_2S_2Br_2 \cdot 2H_2O$. Calculated %: Br 30.77; H_2O 6.9.

A sample of the di-(methyl bromide) derivative in aqueous solution was treated with an aqueous solution of bromine of known concentration. The bromine water was added until the orange microcrystalline precipitate ceased to separate out. At this point somewhat more than 2 moles of bromine had been added. The precipitate was dried over phosphorus pentoxide. On heating to 200°, it began to lose bromine and it decomposed at a higher temperature. The substance is sparingly soluble in water but, on boiling, it passes into solution and does not precipitate on cooling.

Found %: Br 58.30, 58.07. $C_{18}H_{16}N_2S_2Br_6$. Calculated %: Br 59.60.

The low bromine content is apparently explained by the fact that it is very weakly bound. The absorption curve of the hexabromide coincides almost precisely with the absorption curve of the initial dibromide.

ω,ω'-p-Dichloroxylene was prepared by chlorinating p-xylene in carbon tetrachloride [6] and by chloromethylating benzyl chloride with dichloromethyl ether [7]. The second method proved the more rapid and convenient.

p-Phenylenediacetic acid was obtained from ω,ω'-p-dichloroxylene via p-phenylenediacetonitrile and was converted into the acid chloride, with m.p. 66.5° [8], by the action of thionyl chloride.

Di-(methyl chloride) derivative of ω,ω'-bis-(benzothiazol-2-yl)-p-xylene (V). A solution of 8.51 g of p-phenylenediacetic acid chloride in 30 ml of dry benzene was added dropwise with stirring and ice cooling to a solution of 10.22 g of o-aminothiophenol in 70 ml of benzene. A white precipitate was formed right from the first drops. After the addition, the mixture was heated for 10 minutes on the water bath, and then the precipitate was separated, washed with benzene, and dried in the air. The yield of unpurified product was 18.6 g (100%). After crystallization from 150 ml of alcohol 14.85 g of a colorless crystalline substance with m.p. 279-280° was obtained. The salt contains about two molecules of water of crystallization, but on drying in vacuo, it loses not only water but, in part, hydrogen chloride. It was therefore converted by the action of sodium perchlorate into the sparingly cold-water-soluble perchlorate.

The diperchlorate formed white needles and after crystallization from water had m.p. 316-318° (with decomposition).

Found %: Cl 11.96, 12.12. $C_{24}H_{22}O_2N_2S_2Cl_2$. Calculated %: Cl 11.79.

ω,ω'-Bis-(3-methylbenzothiazol-2-ylidene)-p-xylene (VI). An aqueous solution of the dichloride (V) was treated with a slight excess of alkali while being heated on the water bath. The yellow precipitate was separated, washed with water, and dried in vacuo over phosphorus pentoxide. After crystallization from toluene, it formed golden needles with m.p. 261-262°. The yield was 70%.

Found %: N 7.18, 7.18. $C_{24}H_{20}N_2S_2$. Calculated %: N 7.01.

Di-(methyl bromide) derivative of 1,4-bis-[(benzothiazol-2'-yl)-methylene]-cyclohexadiene (VII). A chloroform solution of 1 mole of bromine was added to a solution in chloroform of a sample of the preceeding base. The red-violet precipitate formed was separated off and washed with chloroform. On standing in the air, the product assumed a yellow-green color. The salt is soluble in water with the formation of a turbid solution as a result of partial hydrolysis. On crystallization from water slightly acidified with hydrobromic acid, small yellow-orange crystals with m.p. 216-217° (with decomposition) were obtained.

Found %: Br 26.25, 26.27; H_2O 9.20. $C_{24}H_{20}N_2S_2Br_2 \cdot 3H_2O$. Calculated %: Br 26.01; H_2O 8.79.

SUMMARY

The bis-methylene bases (II) and (VI) are capable of adding halogens ionogenically. In this reaction they behave like divalent metals, reducing the halogen atoms to anions and taking up positive charges with the simultaneous rearrangement of the bonds.

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SYNTHESIS OF DIARYL PHOSPHATES AND ARYL PHOSPHONATES AND SOME OF THEIR PROPERTIES

K. A. Petrov, É. E. Nifant'ev, and R. F. Nikitina

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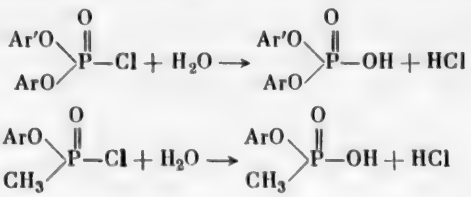
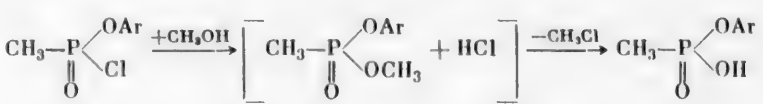
The acid esters of aliphatic alcohols and acids of quinquevalent phosphorus are relatively well studied substances which find practical use. However, in some cases the use of these substances meets with difficulties due to their tendency to undergo changes in the presence of impurities on storage, particularly at high temperatures [1,2].

The present investigation was devoted to the synthesis and investigation of the properties of little-studied diaryl phosphates and the practically unknown monoaryl phosphonates with the purpose of finding stable compounds.

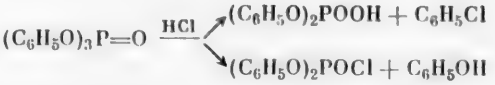
The experiments carried out showed that these substances may be synthesized in good yields by two methods used earlier in the preparation of the analogous compounds of the aliphatic series. According to the first method, they were obtained by the hydrolysis of diaryl phosphoro-chloridates and aryl methylphosphonochloridates.



In the second method, the substances were obtained by the dealkylation of diaryl methyl phosphates and aryl methyl methylphosphonates using hydrogen chloride. As a rule, the intermediate phosphates and phosphonates were not isolated. The whole synthesis was carried out as follows: the alcohol was added to the appropriate acid chloride with cooling and the reaction mixture was heated in a sealed tube.



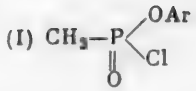
In contrast to the intermediate phosphates containing even one alkoxyl group, triaryl phosphates dearylate under more severe conditions, with the formation of a mixture of substances: thus, triphenyl phosphate yields chlorobenzene and phenol.



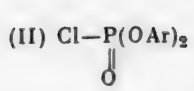
All the acid phosphates and phosphonates which we obtained are shown in Table 2. The purity of the substances were determined by elementary analysis and potentiometric titration. The phosphorochloridates and phosphonochloridates were obtained by heating phenols with phosphoryl chloride and the dichloride of methylphosphonic acid. Mixed phosphorochloridates were synthesized by the reaction of phenols with aryl phosphorodichloridates, which are formed in substantial amounts. In the preparation of diaryl phosphorochloridates. The phosphorochloridates which we obtained are shown in Table 1.

The acid aromatic phosphates and phosphonates are solid and liquid substances, sparingly soluble in water and readily soluble in alkalis, which titrate as monobasic acids. The acid phosphates are freed from impurities by reprecipitation with mineral acids from alkaline solutions previously washed with organic solvents, and also by recrystallization.

TABLE 1. Synthesis of Phosphorochloridates and Phosphonochloridates



(I)



(II)

Type	Ar	Yield in (%)	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	found	calculated	found	calculated
I	Phenyl	50	153–155°(21)	1.5242	1.2392	16.13	16.35	18.59	18.61
I	p-tolyl	61	162–165 (20)	1.5180	1.2378	–	–	17.74	17.70
I	o-tolyl	56	160–163 (18)	1.5205	1.2520	15.02	15.21	17.51	17.70
I	m-tolyl	54	163–165 (24)	1.5205	1.2470	–	–	17.32	17.70
I	4-chloro-3-methylphenyl	51	185–187 (20)	1.5370	1.3549	12.75	12.95	29.32	29.75
II	Phenyl	52	210–212 (24)	1.5473	1.2960	–	–	13.48	13.25
II	p-tolyl	67	231–234 (22)	1.5429	1.2379	10.71	10.45	12.21	12.05
II	o-tolyl	60	220–223 (22)	1.5460	1.2443	10.57	10.45	12.12	12.05
II	m-tolyl	70	228–230 (22)	1.5463	1.2414	10.19	10.45	11.09	12.05
II	4-chloro-3-methylphenyl	82	155–158 (5)	m.p. 40–41°		8.68	8.49	29.18	29.00
II	*	66	222–225 (23)	1.5149	1.2881	11.33	11.01	12.05	12.55
II	**	54	242–245 (24)	1.5571	1.3470	9.89	9.78	22.70	22.56

* Unsymmetrical phosphorochloridate, Ar = phenyl and p-tolyl.

** Unsymmetrical phosphorochloridate, Ar = phenyl and 4-chloro-3-methylphenyl.

TABLE 2. Synthesis of Diaryl Phosphates and Aryl Methylphosphonates

(I) $CH_3-P(=O)(OAr)(OH)$ (II) $HO-P(=O)(OAr)_2$

Type	Ar	Melting point	n_D^{20}	Equivalent point			
				found	calc.	found	calc.
I	Phenyl-	32–33°	–	17.84	18.05	178	172
I	p-tolyl	78–79	–	16.84	16.68	189	186
I	o-tolyl	–	1.5214	16.22	16.68	190	186
I	m-tolyl	–	1.5230	17.02	16.68	189	186
I	4-chloro-3-methylphenyl	93–95	–	13.68	14.05	219.4	220.5
II	Phenyl*	62–63	–	12.05	12.40	254	250
II	p-tolyl**	75–76.5	–	11.69	11.30	278	278
II	o-tolyl	–	1.5475	11.21	11.30	279	278
II	m-tolyl	–	1.5458	11.05	11.30	279.5	278
II	4-chloro-3-methylphenyl	114–116	–	9.35	8.95	339	347
II	***	–	1.5472	12.21	11.75	268	268
II	****	31–33	–	10.28	10.39	300	298.5

* Literature data: b.p. 56° [5], 61-62° [6].

** Literature data: b.p. 80.5-81.5° [7].

*** Unsymmetrical phosphate, Ar = phenyl and p-tolyl.

**** Unsymmetrical phosphate, Ar = phenyl and 4-chloro-3-methylphenyl.

Analogously to the dialkyl phosphates [3], the diaryl phosphates possess arylating properties. On heating some compounds of this series with sodium bromide, the corresponding bromo derivatives are obtained, for example

$$(C_6H_5O)_2PO(OH) \xrightarrow{NaBr} C_6H_5Br.$$

In the given case, in addition to bromobenzene, phenol is always obtained in an amount of about 30% of the weight of bromobenzene. On treating diaryl phosphates with amines (diethylamine and aniline), reaction proceeds sluggishly and arylation products and phenol are obtained in small amounts.

The diaryl phosphates and aryl phosphonates do not undergo disproportionation (ester exchange) even on comparatively long heating, as is shown by the example of diphenyl phosphate, di-p-cresyl phosphate, and p-cresyl methyl phosphonate: these substances underwent absolutely no change either on heating for 10 hours to 100° or on heating for 2 hours to 140°; change takes place only on heating for 4 hours to 140° and is not associated with the appearance of polybasic acids, since the potentiometric titration curves had no additional jumps. However, the titration equivalent was higher than the calculated value. Evidently, the change taking place in the material is not associated with ester exchange but is a consequence of a polycondensation process taking place through the hydroxyl group of the acid and a hydrogen atom of an aromatic nucleus.

EXPERIMENTAL PART

Aromatic ester-chlorides of methylphosphonic acid. In a flask with a reflux condenser and a thermometer were placed 0.75 moles of the dichloride of methylphosphonic acid and 0.75 moles of phenol, and the mixture was slowly heated to 160° and maintained there until the evolution of hydrogen chloride ceased. The reaction products were isolated by fractional distillation in vacuo. The results are given in Table 1.

Diaryl phosphorochloridates. In a flask with a reflux condenser and a thermometer were placed 0.5 moles of phenol and 0.25 moles of phosphorylchloride, and the mixture was slowly heated to 260° and maintained there until the evolution of hydrogen chloride ceased. Data on the diaryl phosphorochloridates obtained after vacuum distillation are given in Table 1.

Diaryl phosphorochloridates with different aryl groups. In a flask with a reflux condenser and thermometer were placed 0.5 moles of an aryl phosphorodichloridate and 0.6 moles of phenol, and the mixture was heated for 4 hours to 190°. Data on the phenyl aryl phosphochloridates obtained after vacuum distillation are given in Table 1.

Diaryl phosphates and aryl phosphonates. A. In a flask with a stirrer was placed 0.15 moles of the appropriate acid chloride, and 35-45 ml of water was added. After half an hour's stirring at 20-25°, the reaction mixture was heated for some minutes to 70-80°, the aqueous layer was separated, and the organic layer weakly basified with 20% caustic soda. Then the solution was acidified, whereupon the acid phosphate or phosphonate, contaminated with inorganic salts, separated. The reaction product was carefully washed free of inorganic substances and crystallized from petroleum ether or alcohol or dried azeotropically with benzene. The yields were close to quantitative.

B. A cooled mixture of 0.5 mole of the appropriate acid chloride and 0.51 mole of anhydrous methanol was sealed in a tube and kept at 95-100° for 8-10 hours. After removal of the methyl chloride, the residue formed a practically pure acid. The yield was close to quantitative. Data on the compounds obtained are given in Table 2.

Reaction of triphenyl phosphate with hydrogen chloride. A mixture of 5 g of triphenyl phosphate and 0.45 g of hydrogen chloride was heated in a sealed tube on the boiling water bath for 5 hours. Then the mixture was poured into water, and the oil was extracted with ether and distilled. A substance with b.p. 40-95° (20-30 mm) (1.6 g) was obtained. From the smell and the intensive coloration given by a sample of the substance with an aqueous solution of ferric chloride, phenol was identified. The main part of the fraction obtained was washed with alkali, dried, and distilled. Chlorobenzene was obtained; b.p. 40-41° (25 mm), n_D^{20} 1.5250 (literature data [4]: b.p. 99-100° (290 mm), 45° (30 mm), n_D^{20} 1.5248).

Reaction of diphenyl phosphate with sodium bromide. A mixture of 5 g of diphenyl phosphate and 2.5 g of sodium bromide was heated in a Wurtz flask (with distillation). The distillate collected at 160-185° was fractionated, and 2 g (63%) of bromobenzene, with b.p. 156-157° and n_D^{20} 1.5631, and 0.7 g (20%) of phenol, with b.p. 180-182°, m.p. 42-43° (a mixed melting point with a known sample gave no depression of the melting point) were obtained. Literature data: for bromobenzene, b.p. 155-156°, n_D^{20} 1.5625 [8]; for phenol, b.p. 182°, m.p. 41° [9].

Reaction of di-p-cresyl phosphate with sodium bromide. In a similar manner to that described above, 3.3 g of di-p-cresyl phosphate and 1.3 g of sodium bromide yielded traces of p-cresol and 1.5 g (20.3%) of p-bromotoluene, with b.p. 182-184°, m.p. 26-27°. Literature data: b.p. 184°, m.p. 28.5° [10].

SUMMARY

1. Diaryl phosphorochloridates have been obtained by the reaction of phosphoryl chloride and aryl phosphoro chloridates and aryl methylphosphonates by the reaction of the dichloride of methylphosphonic acid, with phenols, and these compounds have been converted by hydrolysis or controlled dealkylation into diaryl phosphates and aryl methylphosphonates.

2. It has been shown that diaryl phosphates possess arylating properties.

3. It has been established that, on heating with hydrogen chloride, triphenyl phosphate is dearylated with the formation of a mixture of phenol and chlorobenzene.

4. It has been shown that diaryl phosphates and monoaryl phosphonates do not undergo ester exchange on heating.

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A NEW SYNTHESIS OF DIALKYL PHOSPHATES

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The dialkyl phosphates, like many other organophosphorus substances, are now finding practical use. Thus, for example, they are used for the extraction and separation of the rare-earth elements [1]. Several methods have now been developed for the synthesis of the dialkyl phosphates. However, they are most frequently obtained by the hydrolysis of the corresponding dialkyl phosphorochloridates [2,3] or pyrophosphates [3,4], and also by the controlled dealkylation of mixed full esters of phosphoric acid by hydrogen chloride [5]. These methods, differing, in simplicity, have fundamental disadvantages: the substances are contaminated with the intermediate phosphates and with monoalkyl phosphates and even phosphoric acid, formed under the conditions of synthesis in consequence of the disproportionation of the dialkyl phosphates (ester exchange).

The object of the present investigation is to seek a new method of synthesis of the dialkyl phosphates and to study their properties. It has been established that, notwithstanding data in the literature [6], the dialkyl phosphates are conveniently obtained by the oxidation of the readily-available dialkyl phosphites [7] with oxides of nitrogen:

$$(RO)_2POH \xrightarrow{N_2O_4} (RO)_2PO(OH).$$

This reaction proceeds very readily, and the yields of dialkyl phosphates are close to quantitative. The substances obtained are monobasic acids and are practically free from contamination with neutral substances and polybasic acids, as is shown by potentiometric titration. The compounds containing radicals from C_1 to C_7 are liquids of which some can be distilled in a high vacuum; the magnitudes of the surface tension at the vapor–liquid interface were found and the parachors calculated. The dialkyl phosphates containing the radicals from C_8 and above are solid substances which crystallize from the usual organic solvents.

TABLE 1. Dialkyl Phosphates $(RO)_2PO(OH)$

R	Boiling point at 10^{-4} mm, or melting point	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Equiv. wt. found	Equiv. wt. calc.	Surface tension (dyne/cm)	Parachor found	Parachor calc.	%P found	%P calc.
CH_3	78—80°	1.4080	1.3451	23.08	23.44	128	126	42.796	239.6	237.9	24.22	24.6
C_3H_7	93—95	1.4252	1.1041	42.08	41.79	184	182	—	—	—	17.12	17.01
C_6H_{13}	133—138	1.4350	1.0180	64.17	71.82	264	266	27.387	597.7	621.1	11.99	11.65
C_7H_{15}	—	1.4383	1.0023	77.06	81.06	294.5	294	27.633	674.2	705.1	10.18	10.53
C_8H_{17}	m.p. 29—30°	—	—	—	—	319.4	322	—	—	—	10.04	9.57
$C_{10}H_{21}$	m.p. 46—47	—	—	—	—	381	378	—	—	—	7.77	8.20
$C_{16}H_{33}$	m.p. 68—70	—	—	—	—	540	546	—	—	—	5.79	5.67

The view has been expressed in the literature that the dialkyl phosphates are thermally unstable [8]. We have studied this question in detail and have shown that they undergo no change on heating for several hours to 100°. However, it must be noted that the results obtained relate only to those substances which are absolutely pure (purified by vacuum distillation or recrystallization). If dialkyl phosphates are heated in the presence of acid catalysts or even stored in the presence of traces of the latter, disproportionation of the radicals ensues. (Table 2). Thus, for dialkyl phosphates ester exchange depends not on thermal factors but on the catalytic influence of acidic materials.

TABLE 2. Ester Exchange of the Dialkyl Phosphates $(RO)_2PO(OH)$

R	Catalyst	Time (in hours)	Composition of the mixture (in %)		
			$(RO)_2PO(OH)$	$ROPO(OH)_2$	$(RO)_3PO$
CH_3	—	6 months*	100	—	—
CH_3	—	2.5	100	—	—
CH_3	—	5	100	—	—
CH_3	HCl	2	45	29.2	5.8
C_6H_{13}	N_2O_4 **	5 months*	64	23	15
C_8H_{17}	N_2O_4 **	5 months*	60.5	35	4.5
$C_{10}H_{21}$	—	2.5	100	—	—
$C_{10}H_{21}$	—	5	100	—	—
$C_{10}H_{21}$	—	10	100	—	—
$C_{10}H_{21}$	H_2O	5	100	—	—
$C_{10}H_{21}$	N_2O_4 **	1	76	20.1	3.9
$C_{10}H_{21}$	N_2O_4 **	48*	100	—	—
$C_{10}H_{21}$	HCl	2	56	32	13.5
$C_{10}H_{21}$	CH_3COOH	48*	100	—	—

* The substance was kept at room temperature.

** Traces of oxides of nitrogen.

EXPERIMENTAL PART

Oxidation of dialkyl phosphites. In a wide test tube with a thermometer, a calcium chloride tube and a bubbler reaching to the bottom was placed 15-20 ml of dialkyl phosphite; the tube was cooled with snow and salt, and nitrogen dioxide in a current of inert gas* was passed in such a way that the temperature in the tube was 20-30°. The end of the reaction was determined by the appearance of a green color in the solution. After 4-5 hours' standing the excess of oxides of nitrogen was blown off with dry inert gas, and the substance was placed in a Wurtz flask and maintained under the vacuum of a water-jet pump (the air drawn through was dried in the column with phosphorus pentoxide). After 7-10 hours, the substance was practically pure. The yield was close to quantitative. The properties of the substances obtained are given in Table 1.

In the case of dicetyl phosphite, the reaction was carried out in carbon tetrachloride solution.

Study of ester exchange. The substance, pure or with appropriate additions (0.1-0.5% by weight), was heated at 100° in a closed vessel, and then titrated potentiometrically in 95% alcohol (LP-58 potentiometer with vacuum tube amplifier). The results obtained are given in Table 2.

SUMMARY

1. It has been shown that dialkyl phosphates are produced in good yields by the oxidation of dialkyl phosphites with oxides of nitrogen.

2. It has been established that dialkyl phosphates possess comparatively good thermal stability: they undergo "ester exchange" only in the presence of acidic catalysts.

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* A U-tube filled with phosphorus pentoxide and glass wool and also containing 5 ml of liquid oxides of nitrogen was connected to the bubbler. At room temperature, the oxides of nitrogen gradually evaporated and were carried into the reaction vessel in a current of inert gas.

THERMAL DECOMPOSITION OF TETRAETHYL-LEAD, HEXAETHYLDIPLUMBANE AND THEIR ANALOGS

V. DECOMPOSITION AND DISPROPORTIONATION REACTION OF HEXAETHYLDISTANNANE

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We showed earlier that hexaethyldiplumbane may decompose in two ways. The pure substance and solutions of it in inert media decompose with the formation of tetraethyl-lead and gaseous products [1,2].

$$(C_2H_5)_6Pb_2 \longrightarrow (C_2H_5)_4Pb + Pb + 2C_2H_5 \cdot \quad (I)$$

In the presence of catalytic amounts of certain substances, (aluminium chloride, triethyl-lead chloride, dibromoethane, and similar substances) a different picture is observed. In this case, disproportionation of the hexaethyldiplumbane takes place [3].

$$2(C_2H_5)_6Pb_2 \longrightarrow 3(C_2H_5)_4Pb + Pb \quad (II)$$

It was of interest to establish whether this dual decomposition is a property of hexaethyldiplumbane alone or whether this phenomenon has a more general character and, in particular, is inherent in hexaethyldistannane.

There is no indication in the literature of any possibility of the decomposition of hexaethyldistannane according to an equation analogous to (I). The disproportionation reaction for compounds of the type R_6Sn_2 is known. However, no methods are given in the literature for carrying it out on the case of hexaethyldistannane. The study of the decomposition and the disproportionation reactions of hexaethyldistannane is interesting also from another point of view. We found, by the kinetic method [1,2], that reaction (I) has a complex character and proceeds with the intermediate formation of diethyl-lead. It appeared probably that in the course of reaction (II) a series of intermediate unstable organolead compounds is formed. However, precisely because of their extreme instability, it proved impossible to demonstrate this fact. It is known that organotin compounds are more stable than the corresponding organolead compounds. It is logical to assume that the intermediate products of the disproportionation reaction of hexaethyldistannane will also be quite stable; hence, hexaethyldistannane may proved to be a more convenient subject for studying the mechanism of this reactions.

Procedure. The thermal decomposition and disproportionation reaction of hexaethyldistannane were carried out in sealed evacuated tubes. Hexaethyldistannane, synthesized according to the prescriptions of [4], after repeated fractionating in a current of hydrogen had b.p. 159-160° at 23 mm; n_D^{20} 1.4395. Filling the pure product into the tubes and freeing the tubes from atmospheric oxygen was carried out by the procedure described earlier [2].

The tubes were held at a predetermined thermostatically controlled temperature for a definite time and were then cooled in liquid nitrogen. After this the tubes were connected with a gas burette and opened. Analysis of the gases was carried out by gas chromatography. The liquid part of the reaction mixture was decanted from metallic tin and analyzed spectrophotometrically. The metallic tin was repeatedly washed with ether, dried and weighed.

Results obtained and discussion of them. It was established that hexaethyldistannane containing no impurities does not undergo any change on heating to 235° for 10 hours. On raising the temperature to 260°, thermal decomposition of the material is observed according to the equation.

$$(C_2H_5)_6Sn_2 \longrightarrow (C_2H_5)_4Sn + Sn + 2C_2H_5 \cdot \quad (III)$$

To prove the correctness of Equation (III), the ratio between the amounts of tin deposited and the volume of gas liberated at 285° was studied. It was shown that, with a degree of decomposition of 60-70%, for 1 g-atom of metallic tin there were 1.51-1.60 moles of a gaseous mixture of the following percentage composition: ethane 59.3, 63.0; ethylene, 39.4, 32.0; butane, 0.7, 4.7. It it is assumed that the ethane and ethylene are formed as the result of the disproportionation of ethyl radicals, their amounts should be equal. A disturbance of this equality, so it appears to us, may take place as a result of a partial reaction of the ethylene with ethyl radicals with the formation of non-gaseous products. The possibility of such a type of reaction follows from the work of Cramer [5] on the thermal decomposition of tetraethyl-lead in the presence of ethylene under conditions close to ours. The amount of polymeric material in our case cannot exceed 0.01 g and cannot be demonstrated experimentally. However, if it is assumed that part of the ethylene is lost in this way, about 1.9 moles of the gaseous mixture will be obtained per 1 g-atom of tin deposited, which agrees well with Equation (III). In addition, it must be emphasized that Equation (III) describes only the total process, and does not indicate its mechanism.

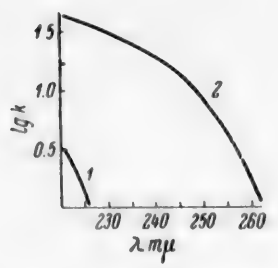

Fig. 1. Adsorption spectra of tetraethyltin (1) and Hexaethyldistannane (2). ([k] = g^{-1} · liter · cm^{-1}).

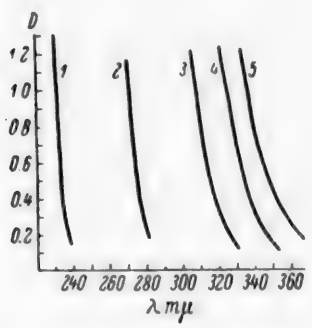

Fig. 2. Spectrophotometric adsorption curves (thickness of the cell, 0.020 mm). 1) Tetraethyltin; 2) hexaethyldistannane; 3) hexaethyldistannane after partial decomposition (20 min at 275°); 4) hexaethyldistannane after partial decomposition (60 min at 275°); 5) hexaethyldistannane after partial decomposition (60 min at 280°).

In a study of the ultraviolet absorption spectra of tetraethyltin and hexaethyldistannane carried out in the SF-4 spectrophotometer, a difference between them in the region from 220-300 mμ was found (Fig. 1). By means of a systematic spectrophotometric check on the decomposition of hexaethyldistannane this enabled some ideas in the mechanism of the process to be formed.

As can be seen from Fig. 2, the spectrophotometric absorption curve for hexaethyldistannane is found in the long wavelength region of the spectrum in comparison with the corresponding curves for tetraethyltin. Hence, if Equation (III) accurately represented its mechanism, characterized by a continuous increase in the optical density of the reaction mixture through the dilution of the hexaethyldistannane by the tetraethyltin formed.

As a result, the absorption curves of hexaethyldistannane subjected to partial decomposition should be in the region bounded by the spectrophotometric absorption curves of pure samples of tetraethyltin and hexaethyldistannane. However, experiments showed that the initial stages of the decomposition are characterized not by a diminution, but by a sharp increase in the optical density of the reaction mixture (Fig. 3). As a result, the spectrophotometric absorption curves of incompletely decomposed samples of hexaethyldistannane are strongly displaced to the long wavelength region of the spectrum in comparison with the absorption curve of pure hexaethyldistannane (Fig. 2). This fact can be explained only by the appearance of an intermediate decomposition product absorbing strongly in the long wavelength regions of the spectrum. This intermediate product may be diethyltin or a low-molecular-weight homolog of it. High-molecular-weight compounds of the type of $[Sn(C_2H_5)_2]_n$, as will be shown below, being insoluble in tetraethyltin, separate from it and decompose at relatively low temperatures, which does not take place in the present case.

Thus, as in the case ofhexaethyldiplumbane [1], the thermal decomposition of hexaethyldistannane is more correctly represented not by Equation (III), but by a combination of the following equations:

$$(C_2H_5)_6Sn_2 \longrightarrow (C_2H_5)_4Sn + Sn(C_2H_5)_2 \quad (IV)$$

$$Sn(C_2H_5)_2 \longrightarrow Sn + 2C_2H_5 \cdot \quad (V)$$

The formation of an intermediate product in the decomposition of hexaethyldistannane is also confirmed by the following facts. 1) A regular change in the optical density of the reaction mixture is observed during the decomposition (Fig. 3). The shape of the kinetic curves can be explained only by the presence of an intermediate decomposition product. 2) Tetraethyltin and hexaethyldistannane are colorless compounds. During thermal decomposition, hexaethyldistannane assumes the yellow color characteristic for diethyltin and retains it at room temperature, in the absence of air, for several years. On contact with air, a rapid decolorization of the reaction mixture and the formation of diethyltin oxide is observed. The appearance of the color must be due to the resinification of the product, since its intensity changes in parallel with the change in the optical density of the reaction mixture: the color deepens with a rise in the optical density, then fades, passing through a maximum.

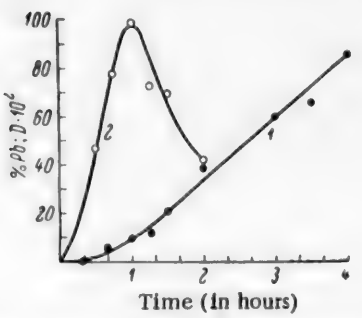

Fig. 3. Kinetic curves for the decomposition of hexaethyldistannane at 275 ± 0.6°. 1) Accumulation of metallic tin in the reaction mixture (in % of theoretical); 2) change in the optical density (D) of hexaethyldistannane during its decomposition (cell thickness 0.020 mm, wavelength 325 mμ).

It follows, from all that has been said, that the courses of the reactions observed in the thermal decomposition of hexaethyldiplumbane and hexaethyldistannane are very similar. Experiment shows that the similarity and chemical properties of the compounds under consideration is not limited to the thermal decomposition reaction. In particular, the processes taking place with hexaethyldiplumbane [3] and hexaethyldistannane under the action of catalytic amounts of chlorides of certain metals ($AlCl_3$, $TiCl_4$, $ZrCl_4$, $SnCl_4$, and the like) are extremely similar. It has already been mentioned above that the thermal decomposition of hexaethyldistannane takes place at a considerable velocity, beginning at 260°. With the addition of 1-2% (by weight) of catalyst, the decomposition of hexaethyldistannane is observed even at 70-80°. The performance of the process in sealed evacuated tubes connected with a mercury manometer shows that the reaction is not accompanied by the formation of gas and may be represented by the equation

$$2(C_2H_5)_6Sn_2 \longrightarrow 3(C_2H_5)_4Sn + Sn. \quad (VI)$$

In contrast to the process of disproportionation of hexaethyldiplumbane, where the presence of intermediate products could not be shown, on carrying out reaction (VI) under mild temperature conditions (70-75°) the formation of intermediate substances can be established by the appearance of an intense cherry-red color and the subsequent stratification of the reaction mixture. Analysis of the upper, colorless layer shows that it consists mainly of tetraethyltin. The composition of the separated heavy viscous dark red liquid corresponds to diethyltin [$Sn(C_2H_5)_2$] containing a certain amount of catalyst. Chlorine analysis showed a uniform distribution of the catalyst in the upper and lower layers.

It must be emphasized that the phenomenon of stratification has nothing at all to do with the processes of resin formation, since, after stratification, decomposition of the lower layer is observed. As a result, the sole products of the disproportionation of hexaethyldistannane are tin and tetraethyltin.

The analytical data for the lower layer, and the very fact of the stratification of the reaction mixture, indicate that the reaction proceeds with the intermediate formation of high-molecular-weight organotin substances, which is in harmony with the ideas expressed previously [3,6] on the mechanism of this reaction.

As is known, heating unsymmetrical organometallic compounds of the type of $(C_2H_5)_3SnR$ with catalytic amounts of aluminium chloride or similar substances leads to the redistribution of the radicals [7]. Hexaethyldistannane may be considered a compound of this type, inasmuch as each of the tin atoms in this compound are connected with

three ethyl radicals and one triethyltin radical, $(C_2H_5)_3SnR$, where $R\,(C_2H_5)_3Sn$. It is possible to suppose, also, that both types of radicals take part equally readily in the redistribution reaction. In this case, the intermediate formation of high-molecular-weight organotin compounds in addition to tetraethyltin becomes explicable.

As is known, the redistribution of radicals form all the possible combinations of tetra-alkyl derivatives of tin [7]. Hexaethyldi-stannane must give a mixture of the following compounds: $(C_2H_5)_4Sn$ (A), $(C_2H_5)_3SnR$ (B), $(C_2H_5)_2SnR_2$ (C), $C_2H_5SnR_3$ (D), and SnR_4 (E). It is readily seen that even this basic reaction leads to the formation of quite complex molecules, since compounds (C), (D) and (E) possess chains of three, four and five tin atoms, respectively. In addition, substances (C), (D), and (E), like hexaethyldistannane, may be considered as unsymmetrical organometallic compounds. For example, (C) may be considered as $(C_2H_5)_3SnR'$, where $R' = (C_2H_5)_2SnSn(C_2H_5)_3$. Consequently, it is theoretically probable that (C), (D), and (E) will take part in similar reactions of the redistribution radicals in the course of which, in addition to tetraethyltin, a series of substances with even longer and more branched chains of metal atoms will arise.

Thus, in agreement with the experimental observations, the redistribution of the radicals in hexaethyldistannane must lead to the formation of tetraethyltin and a mixture of high-molecular-weight organotin compounds. In addition, as the organotin molecules become more complicated, so must their thermal stability diminish. Consequently, in the reaction of the redistribution of the radicals, the decomposition of the complex molecules will be observed at comparatively low temperatures. Hence, the final products of the reaction under consideration will be tetraethyltin and metallic tin.

Catalyst	Content of catalyst in the $(C_2H_5)_6Sn_2$ (in % by wt.)	Time of heating in the boiling water bath (in hours)	Yield of Sn (in % of theoretical)
$SnCl_4$	9.5	16	15.2
$ZrCl_4$	5.2	14	100
$TiCl_4$	6.7	12	100
C_2H_5MgBr, C_2H_5HgBr, $(C_2H_5)_3SnCl$, CH_2BrCH_2Br	2.0—4.0	35—40	0

EXPERIMENTAL PART

Disproportionation of hexaethyldistannane. In a tube fused to a mercury manometer [2] were placed 3.46 g of hexaethyldistannane and 0.07 g of anhydrous aluminum chloride (2% on the weight of the hexaethyldistannane). The tube was evacuated to 1 mm Hg residual pressure, sealed and immersed completely in the boiling water bath. After 10 hours' heating, the absence of gas formation was ascertained. The tube was opened, and the reaction mixture was decanted from metallic tin and distilled. A yield of 2.44 g (82.4%) of tetraethyltin, with b.p. 176-178°, n_D^{20} 1.4724, was obtained. The metallic tin was washed with acetone and ether and dried. It amounted to 0.05 g. The yield was quantitative. The effectiveness of other catalysts may be judged from the data in the table.

Disproportionation of hexaethyldistannane under mild conditions. A mixture of 5.80 g of hexaethyldistannane and 0.16 g of anhydrous aluminum chloride (~ 2.8% on the weight of hexaethyldistannane) in an evacuated tube was held thermostatically at 70° for 1 hour. During this time, the initially colorless mixture assumed a cherry-red color. Then it decomposed. The tube was cooled in an ice bath and opened. The upper colorless layer was decanted rapidly from the heavy viscous dark red liquid.

Analysis of the upper layer. Found%: C 39.21; H 8.03; Sn 51.61; Cl 1.01. $(C_2H_5)_4Sn$. Calculated %: C 40.90; H 8.56; Sn 50.53.

Analysis of the lower layer. Found %: C 25.68; H 3.26; Sn 68.81, 70.00; Cl 1.10. $[(C_2H_5)_2Sn]_n$. Calculated %: C 27.17; H 5.68; Sn 67.14.

The lower layer was oxidized by atmospheric oxygen with a great evolution of heat. The oxidation product was a colorless infusible mass. When the stratified reaction mixture or the lower layer was heated in a thermostat without access of air for a long time, it decomposed with the formation of tin and tetraethyltin. The results of elementary analysis of the lower layer (higher tin content than calculated) allowed it to be assumed that a decomposition process accompanies the reactions of the hexaethyldistannane molecules to form more complex substances.

SUMMARY

1. It has been shown that the thermal decomposition of hexaethyldistannane proceeds with the intermediate formation of diethyltin or its low-molecular-weight homologs. The final decomposition products are tetraethyltin, tin and a mixture of gaseous substances.

2. It has been established that heating hexaethyldistannane with catalysts of the type of aluminium chloride leads to disproportionation. It has been shown that this reaction proceeds with the intermediate formation of a mixture of high-molecular-weight organotin compounds. A hypothesis on the mechanism of this reaction has been put forward.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

THE REACTION OF BENZALDEHYDE WITH AMMONIA

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and A. I. Finkel'shtein

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In the reaction of aliphatic aldehydes with ammonia, the products with a molar ratio of 1 : 1 (aldehyde-ammonias) first formed split out water and form aldimines, which are unstable and finally form the stable cyclic hexahydrotriazines. Thus, the final product from the reaction of acetaldehyde with ammonia is 2,4,5-trimethyl-1,3,6-hexahydrotriazine. [1].

There is no information in the literature on an analogous reaction of aromatic aldehydes with ammonia. It is known only that aldehydes not possessing α-hydrogen atoms form with ammonia, under the usual conditions, solid products – the so-called hydramides [1].

$$3C_6H_5CHO + 2NH_3 \longrightarrow C_6H_5CH{=}N{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}N{=}CHC_6H_5 + 3H_2O$$

(I)

Francis [2] has shown that, on cooling a mixture of benzaldehyde, ethyl alcohol, and concentrated aqueous ammonia to -20°, a crystalline substance with m.p. 45° of the composition $C_{14}H_{15}O_2N$ (II) separates, this substance being unstable and slowly decomposing on standing into hydrobenzamide (I), benzaldehyde and water. The author maintains that (II) is an intermediate product in the formation of hydrobenzamide at room temperature. However, it has more recently been found [3] that the reaction is bimolecular with respect to the reactants and that the course of the reaction cannot be completely explained by Francis' mechanism.

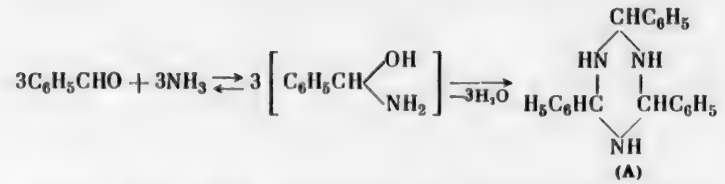
We assumed that there is no difference in principle between reactions with ammonia of aldehydes possessing and not possessing α-hydrogen atoms. In the present work it was shown that, in fact, in the reaction of benzaldehyde with ammonia a compound in the formation of which 3 moles of each of the reactants takes part is first produced.

On slow addition of a solution of benzaldehyde in methyl alcohol to a saturated solution of ammonia in methyl alcohol at -10° with simultaneous passage of ammonia and stirring, we obtained, after the mixture had been allowed to stand (at -10°) a previously unknown crystalline substance of the composition $C_{21}H_{21}N_3$ (III). This compound is relatively unstable. On standing, more rapidly on slight warming or on recrystallization, it loses ammonia and forms hydrobenzamide. Further, in the determination of the molecular weight in benzene, loss of ammonia takes place, in consequence of which the value of the molecular weight obtained, 270-280, is low compared with the 315 calculated for (III).

When ammonium chloride is present in the reaction mixture as catalyst (1.5 g per 25 g of benzaldehyde), the base (III) is formed considerably more quickly than when no catalyst is present. After 2 days (instead of 3) the yield is 83% (instead of 25%). The simultaneous action of 1.5 g of NH_4Cl and 3 g of calcium chloride influences the rate of reaction to an even greater extent: after one day the yield amounts to 96%.

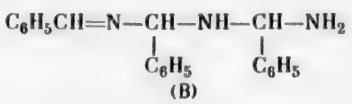
Determination of the neutralization equivalents of the products obtained from benzaldehyde and ammonia by the usual method of synthesis of hydrobenzamide [4] showed that they consist of a mixture of (I) and (III) (equivalent weight 115-130). On recrystallizing this mixture from methyl alcohol, hydrobenzamide was obtained. Thus, the intermediate product in the preparation of hydrobenzamide is (III) and not the compound (II) synthesized by Francis [2]. It must be noted that ammonium chloride exerts a catalytic action also in the production of hydrobenzamide (I) at room temperature [4]. With the addition of ammonium chloride, hydrogenzamide is formed quantitatively in 2.5 hours, and in the absence of a catalyst in 4 hours.

It must be assumed that the production of (III) under the conditions described above takes place through a series of stages without the formation of any stable intermediate products – for example, according to the following scheme.



(A)

According to the scheme given, which is in harmony with a bimolecular mechanism for the reaction between benzaldehyde and ammonia, [3], (III) is 2,4,6-triphenyl-1,3,5-hexahydrotriazine (A) – that is, its structure does not differ from the structure of the product of the reaction of acetaldehyde with ammonia [1]. However, structure (B), which is less probable from the point of view of the reaction mechanism and the possibility of existence, also corresponds to the empirical formula $C_{21}H_{21}N_3$.

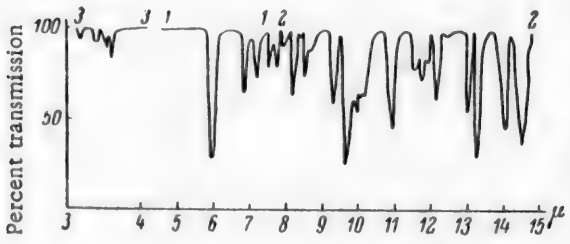


(B)

In order to define the structure of the base (III), its infrared spectrum was taken (see Figure). A series of bands was observed in the region of frequencies for the stretching vibration of N – H and C – H groups (2800-3300 cm^{-1}). The band of highest frequency, with γ_{max} 3180 cm^{-1}, both from its intensity and its frequency, can be assigned only to the NH vibrations of a secondary amine, somewhat displaced towards the low-frequency region under the influence of hydrogen bonds. The double band characteristic for NH_2 groups in this region is absent. Other bands in this region relate to C – H vibrations of the benzene ring and CH groups. One band with a frequency γ_{max} 1680 cm^{-1} is found in the 1600-1700 cm^{-1} region. If the structure of the substance under investigation corresponds to formula (B), then at least two intense absorption bands must be expected in this region (deformation vibration of the NH_2 group and stretching vibration of the C = N bond). The single band observed (deformation NH vibration [5]) can correspond only to structural formula (A).

Thus, the infrared spectrum of compound (III) is in harmony with the structural formula (A) and excludes formula (B).

No substances analogous to (III) could be obtained from salicylaldehyde or furfural: probably they are even more unstable than (III).



Infrared spectrum of the base $C_{21}H_{21}N_3$. 1) NaCl prism, 0.33% in KBr; 2) NaCl prism, 1% in KBr, 3) LiF prism, 0.33% in KBr.

A solution of 25 g of benzaldehyde in 50 ml of methyl alcohol was added over 4 hours, with stirring and with the passage of ammonia, to a mixture of 75 ml of methyl alcohol, 3 g of calcium chloride and 1.5 g of ammonium chloride saturated at -10°. After the mass had been allowed to stand for 24 hours (-10°), white needle-shaped crystals separated out, and these were washed with water and methyl alcohol (50 ml) and dried in the air. A yield of 23 g (96%) of (III) was obtained.

Found %: C 79.74, 80.15; H 6.70, 6.63; N 13.35, 13.40. Equivalent weight 106. $C_{21}H_{21}N_3$. Calculated %: C 79.96; H 6.71; N 13.34. Equivalent weight 105.1.

The infrared absorption spectra were obtained with the IKS-12 spectrometer using lithium floride prisms (for the 2-4 μ range) and sodium chloride prisms (for the 4-15μ range). The substance under examination was pressed in potassium bromide as described earlier [6].

SUMMARY

In the preparation of hydrobenzamide, an intermediate reaction product is the previously unknown compound $C_{21}H_{21}N_3$, formed from benzaldehyde and ammonia in a molar ratio of 3 : 3 and consisting of 2,4,6-triphenyl-1,3,5-hexahydrotriazine.

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STEREOCHEMICAL INVESTIGATIONS

IX. THE SPECTROPOLARIMETRIC DETECTION OF THE TAUTOMERISM OF AMIDES

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As we have already briefly reported [1] we have succeeded in obtaining new information on the existence of tautomeric forms of amides using a simple modification, made in our laboratory, of a photoelectric spectropolarimeter [2].

The first observations in the field of the tautomerism of amides are due to Baeyer [3,4] who, in his investigations devoted to compounds of the indigo group noted that isatin may give derivatives of two types, based on the "lactam" and "lactim" forms. Baeyer considered the stable form of isatin itself to be the "lactim" form with the hydroxyl group in the α-position. Beginning in 1907, Heller [5] began the publication of numerous papers containing information on the various tautomeric forms of isatin and its homologs. At the beginning of the "twenties, a vigorous controversy arose between him and Hantzsch [6,7], who, in a series of papers published in 1921-1925, conclusively demonstrated the incorrectness of Heller's statements on the supposed four isomeric forms of isatin and its derivatives obtained by him: some of the "isomers" proved to be simply impure forms of the same substance, and some were dimerization products. In these papers, Hantzsch completely denied the possibility that the lactam form and its salts containing metal on the nitrogen existed. Without dwelling on all attempts to solve the question of the structure of isatin, we shall mention that in 1940 A. E. Arbuzov [8] showed that, in the action of triphenylmethyl chloride (or bromide) on the silver (or sodium) salt of isatin, tritylisatin is obtained as a mixture of two forms; they have the same melting point but differ in color and in crystalline form, consisting of red prisms and yellow needles. Both forms are readily saponified, which Arbuzov considered an indication of their O-structure, but he does not exclude the possiblity of a tautomeric equilibrium of the O- and N-forms. In 1952, A. E. Arbuzov and M. Sh. Bastanova [9] showed that a series of other derivatives of isatin can also be obtained in two forms.

The second classical subject in which lactam-lactim tautomerism was observed is carbostyril. Friedländer, in particular, has devoted a series of papers to it. While not dwelling in detail on the work on carbostyril, we shall merely mention that in 1952 Arbuzov and Bastanova [11] published a paper on the subject of carbostyril derivatives analogous to their paper on the synthesis of isatin derivatives.

From the end of last century to our own day much effort has been expended on the solution of the question of the structure of simple amides of non-cyclic structure.* Thus, for example Titherley [12] showed that benzamide, like other amides, give two silver salts – a red one and a colorless one. He considered that in both of these the metal is united with the oxygen and unsuccessfully attempted to isolate the free iminol form by the action of dry hydrogen sulfide on a suspension of the colorless silver salt in absolute ether. Other attempts to solve the question of the structure of amides by a chemical method are also known. In particular, Hantzsch [13,14] considered that phosphorus pentachloride or acetyl chloride react with the splitting out of hydrogen chloride only with true, and not with "pseudo" acids. It was a similar state of affairs, in his opinion, with the formation of ammonium salts in an anhydrous medium. Arndt [15] advocated another criterion: he considered that methylation with diazomethane is a reliable method of determining the position of "acid" hydrogen. From the results of the reaction with diazomethane, Arndt, in particular, concluded that lactim forms were present in 4-hydroxycarbostyril [16].

* In this connection, it is appropriate, apparently, to speak in the most general case not of 'lactam-lactim' tautomerism, but of 'amide-iminol' tautomerism, since, as is well known, only cyclic amides are known as lactams.

However, since chemical action is always associated with a displacement of the position of an equilibrium, chemical methods are not, in general, well suited for the investigation of tautomerism systems and must be used with great circumspection. More success may be expected from the use of physical methods, which have also been repeatedly used for the solution of the question of the tautomerism of amides. Thus, Schmidt [17], in considering the question of the structure of amides, attempted to rely on a comparison of boiling points. But, like a number of other authors – for example, Claisen [18] – he also used refractometric data. Neither of these methods gave a conclusive result. Auwers [19], and also Lachman [20], investigated the cryoscopic behavior of amides in benzene and naphthalene, and observed their association; however, they did not decide whether this must be considered an indication of the imino form or not, nor did ebullioscopy give the answer [21].

Giles et al. [22-24], investigating the dependence of the dielectric constant or refractive index in ternary mixtures on the concentration, concluded from the shape of the curves that molecular compounds are formed and, in particular, decided that considerable enolization of amides took place in non-polar solvents. In a study of isatin by the polarographic method [25,26] it was found that six molecular or ionic varieties of this substance were formed at various pH's. In order to explain the polarographic behavior of nitroacetanilide, tautomerism of the amide groups was assumed [27]. An X-ray investigation of crystalline acetamide showed that its molecule exists in the ketone form [28], while in N-acetylglycine the interatomic distances in the crystal were found to be intermediate between those corresponding to the amide and the iminol forms [29]. A similar result was obtained on measuring the electron density of crystalline α-pyridone: it was shown that the hydrogen atom responsible for tautomerism formed an intermolecular hydrogen bond between the nitrogen and the oxygen [30].

The measurement of dipole moments has also been used for the study of the structure of amides [31,32]. From these measurements, in particular, it has been concluded that unsubstituted and mono-substituted amides behave differently on association: while unsubstituted amides dimerize, mono-substituted amides from linear polymers [33-35].

A particularly large number of investigations have been devoted to the investigation of the tautomerism of amides by spectral methods. Hartley and Dobbie [36] were pioneers in this field; they compared the ultraviolet absorption spectra of free isatin and carbostyril with their N- and O-methyl ethers, known to possess the lactam and lactim structures, respectively. Since the spectra of the O-methyl esters, according to their results, proved to be different from the spectra of the N- derivatives and from the spectra of unsubstituted substances closely related to the latter, Hartley and Dobbie concluded that free isatin and carbostyril existed in the lactam forms. However, two decades later, Hantzsch [6], repeating this work, found that the spectra of isatin and its two methyl esters were so similar that he was unable to come to any conclusion on the structure of isatin. A controversy arose, in the course of which Hicks [37], and Morton and Rodgers [38], supported Hantzsch's results, while Marchlewski et al. [39,40] maintained the correctness of the old work of Hartley and Dobbie. Clarity was introduced only in 1935, when Ault, Hirst and Morton [41] published the results of a careful check carried out independently in two laboratories. It was shown that Hantzsch was correct and that the results on the difference in the spectrum of O-methylisatin arose from the fact that Hartley and Dobbie, and after them those authors who supported them, measured not the spectrum of O-methylisatin itself but the spectrum of methyl ester of o-aminobenzoylformic acid formed from isatin as a result of spontaneous ring opening. With respect to carbostyril, Hartley and Dobbie's original conclusion proved to be correct: the absorption spectra does actually show that it exists in the lactam form.

In 1931, Hantzsch [42] used the spectral method to solve the question of the structure of non-cyclic amides. He compared the ultraviolet absorption spectra of trichloroacetamide and benzamide with the spectra of the corresponding derivatives having a fixed amide or iminol structure, and came to the conclusion that in alcoholic solutions these amides exist predominantly in the iminol form. These results were confirmed by other authors [43-45]; however, after almost a quarter of a century, Grob and Fisher [46] repeated and extended this work, investigating the infrared spectra in addition to the ultraviolet spectra, and came to the diametrically opposite conclusion that no iminol form was present. Very recently, Yu. N. Sheinker [47], studying the ultraviolet and infrared spectra of some heterocyclic amides, again interpreted the results obtained as evidence for the existence of the iminol form in alcoholic and aqueous solutions.

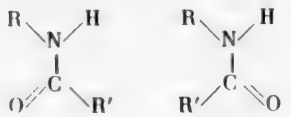
The method of infrared spectroscopy has been used repeatedly in the last 10-15 years for the solution of the question of the structure of amides. Thus, in one of the early American investigations [48] based on the study of the infrared spectrum of N-ethylacetamide, it was concluded that this existed in the iminol form, molecular association taking place in solution according to the scheme:

In contrast to this, unsubstituted amides, in the opinion of the authors of this paper, form chain polymers on association*. Richards and Thompson [49], on the contrary, interpreted the infrared spectra from the point of view of the usual true amide structure. In 1959, Klemperer et al. [50], investigating the infrared spectra of a series of monosubstituted amides in various solvents, confirmed the results of earlier work [48] of their association in the form of chain polymers; however, they did not connect this with the existence of the iminol form.

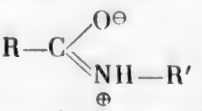
According to D. N. Shigorin's results [51], the Raman spectrum of α-benzoylamine-β-methylcrotonic acid indicates the presence of the iminol form.

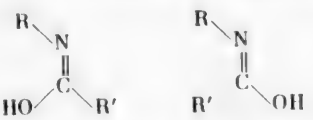
This brief review of the state of the investigation of lactam-lactim (amide-iminol) tautomerism shows that, in spite of the considerable number of investigations in this field, and in spite of the use of the whole arsenal of modern methods, the question still remains extremely complicated, and similar results are frequently interpreted by different authors from completely opposite points of view. In this connection, it is impossible not to recall that many investigators give repeated warnings on the necessity for greater circumspection in the application of physical methods [52-54].

This constant attention to the problem of the structure of the amide group is not casual: this question is connected with the problem of the structure of proteins and polypeptides. At the present time it is universally agreed that the amide group has a plane configuration capable of existing in "trans" form (A) or the "cis" form (B)



(A) (B)

It is considered that the "trans" form predominates (see, for example [55,56]). In particular, Pauling's fruitful idea on the three-dimensional structure of proteins [57] is based on this assumption. To explain the "fixing of the three-dimensional forms (A) and (B) on the basis of the usual amide formula, the idea of mesomerism (or, according to Pauling, resonance) with a polar form of the type  is attractive. Meanwhile, the existence of two three-dimensional isomeric plane structures naturally follows from the iminol formula of amides, the correctness of which has, up to the present, neither been incontrovertibly demonstrated nor conclusively disproved.



The starting point of our work was the measurement of the rotary dispersion of N-benzoyl-α-phenylethylamine (I) in benzene and methanol solutions. It was found that not only did the sign of the dispersion differ but so also did the shape of the spectropolarimetric curve. This result was completely unexpected, since it has been shown in Djerassi's investigations** that the rotatory dispersion curve is characteristic for each substance and does not change while the "near stereochemical enviroment" is maintained. However, in the case of N-benzoyl-α-phenylethylamine, without any apparent change in the "stereochemical environment", but only as the result of a change of solvent, the shape of the rotary dispersion curve was found to be completely reversed. The rotatory dispersion curves for N-benzoyl-α-phenylethylamine in a number of solvents are given in Fig. 1. As can be seen from this figure, from the point of view of their influence on the rotation of N-benzoyl-α-phenylethylamine, solvents may be divided into three types: solvents in which the rotatory dispersion is normal, the rotation having the same sign as the rotation of

* We may recall that from the values of the dipole moments [33-35], exactly the opposite conclusion was arrived at—that N-mono-substituted amides associate to form chains and unsubstituted amides associate to form dimers.

** A review of Djerassi's work is to be found in his recently published book [58]. The only observed case of the dependence of the shape of the dispersion curve (sign of the Cotton effect) on the solvent, for 2-chloro-5-methylcyclohexanone, was explained by Djerassi as due to a change in conformation [59].

the initial amine; solvents in which the rotatory dispersion is normal but the rotation has the opposite sign to the rotation of the initial amine; and solvents in which the shape of the dispersion curve is anomalous. The first type includes benzene, pyridine, and dioxane; the second type includes methanol, acetone, aqueous pyridine, and aqueous dioxane; and the third type includes acetic acid. No direct dependence on the polarity of the solvents is observed in this series; it may rather be assumed that hydroxyl-containing solvents have a specific effect. It is noteworthy that even small additions of water, as special experiments showed, "reverse" the shape of the dispersion curve in pyridine and dioxane solutions.

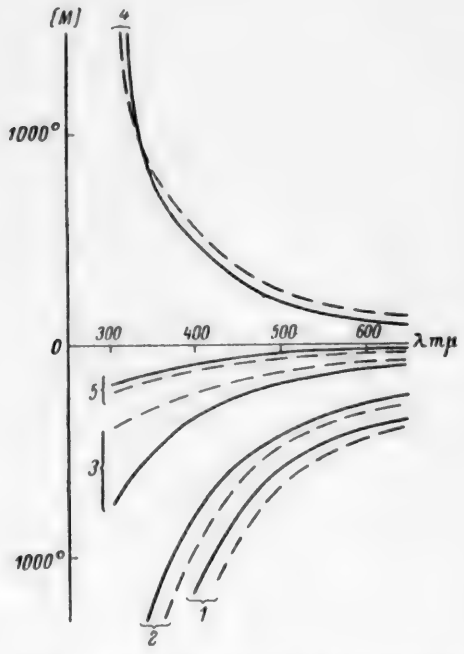


Fig. 1. Rotatory dispersion of N-benzoyl-α-phenylethylamine. 1) In benzene; 2) in methanol; 3) in pyridine, 4) in pyridine with water (1 : 1); 5) in acetic acid; 6) in acetone; 7) in dioxane.

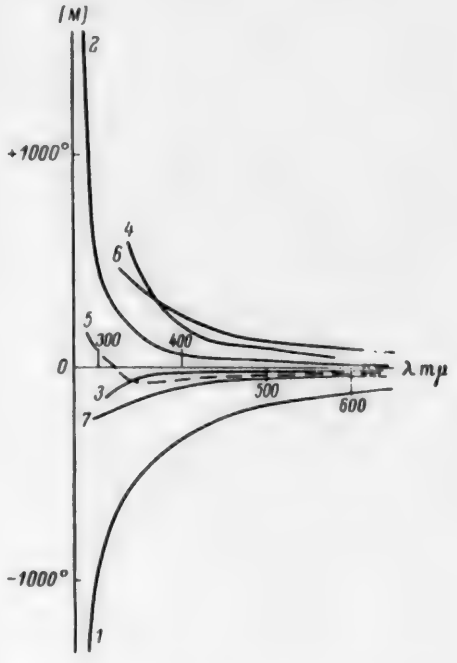
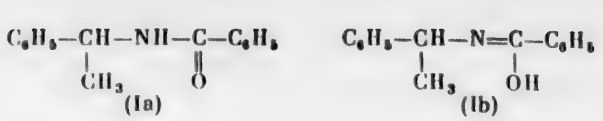


Fig. 2. Rotatory dispersion of derivatives of α-phenylethylamine in methanol (continuous lines) and in benzene (broken lines). 1) N-benzoyl-N-benzyl-α-phenylethylamine (II); 2) N-benzoyl-N-ethyl-α-phenylethylamine (III); 3) N-benzyl-α-phenylethylamine (IV); 4) N-benzal-α-phenylethylamine (V); 5) α-phenylethylamine.

The sharp change in the rotatory dispersion curve lead to the thought that, in the solutions, we are dealing with what are, in essence, different substances. This supposition received independent confirmation by another method. It was found that if N-benzoyl-α-phenylethylamine crystallized from pentane and having m.p. 128-129° was heated for some time in dilute methanol, on cooling, a form having m.p. 123° separated from the solution. By observing the melting process under the microscope, it could be seen that the substance melting at 123° solidified after some time, in spite of a slow rise in the temperature, and then melted again at 128-129°.* Thus, the hypothesis of the existence of two forms is confirmed. Having obtained these two forms, we naturally attempted to observe a difference in their spectropolarimetric behavior. It was found however that the magnitude of the rotation depended only on the nature of the solvent and did not depend on whether the sample used was of the form with m.p. 123° or that with 128°. Apparently, equilibrium is established instantaneously in solution or, in any case, was achieved in the time necessary for dissolving the material, filling the polarimetric tube, and adjusting the temperature (about 5-7 min). As far as concerns the nature of the forms isolated, the most probable assumption is that of amine-iminol tautomerism.

* In the literature different melting points for N-benzoyl-α-phenylethylamine according to the solvent used for recrystallization are also given: 122° (from alcohol) [60] and 125° (from ligroin) [61]. A warning must be given that in the last paper an error was committed in the calculation of the molecular rotation from the specific rotation.



(Ia) (Ib)

If this assumption is true, it must be expected that benzene derivatives of α-phenylethylamine mono-alkylated on the nitrogen [for example, N-benzoyl-N-benzyl-α-phenylethylamine (II) or N-benzoyl-N-ethyl-α-phenylethylamine (III)] will be incapable of passing into a form of the type (Ib), and, consequently, there can be no "solvent effect" similar to that observed with N-benzoyl-α-phenylethylamine with such compounds. In addition, it may be considered that form (Ia) is similar, from the point of view of "near stereochemical environment", to N-benzyl-α-phenylethylamine (IV), and form (Ib) to N-benzal-α-phenylethylamine (V). Consequently, it may be expected that in solvents of one type, the rotatory dispersion curve of N-benzoyl-α-phenylethylamine should be similar to the rotatory dispersion curve of (IV), and in solvents of another type to the rotatory dispersion curve of (V).

The results of the measurements are in complete agreement with these expectations (Fig. 2) and show that N-benzoyl-α-phenylethylamine exists in the tautomeric (iminol) form in hydroxyl-containing solvents and in acetone.

In connection with the detection of the two forms of N-benzoyl-α-phenylethylamine it is impossible not to recall that isolated indications of the presence of two forms in other amides may be encountered in the literature. Thus, for example, Gattermann [62] observed as early as 1890 that the acetyl derivative of m-nitro-p-toluidine crystallized from water in the form of bright yellow needles, and from cold alcohol in the form of colorless crystals. Gattermann also demonstrated the interconversion of the two forms and put forward hypotheses on physical isomerism, the influence of the asymmetric nitrogen, and the tautomerism of the amide group as possible explanations. In 1905, Orlov [63] reported the production of several forms of formanilide and formtoluidine; however, he characterized his materials very superficially. We shall recall also that Timmermans [64] insists that all cases of polymorphism arise as a result of isomerism or tautomerism.

Although, in the light of all that has been said, the explanation of the results we obtained by the assumption of amide-iminol tautomerism is extremely probable, other possible explanations of the observed dependence of the optical rotation on the solvent must be mentioned.

The first of these possible explanations is linked with Bender's observation [65] that, in certain cases, derivatives of acids are capable of forming addition products of the ortho-form type in solution: it might be assumed that such a type of addition product is formed in solutions of N-benzoyl-α-phenylethylamine, strongly affecting its rotation.

A second possible explanation follows from the work mentioned above relating to the association of amides. In fact, it is by association that Nerdel et al. [66] explained the peculiar influence of solvents on the optical rotation of amides of α-phenylethylamine with substituted benzoic acids. It seems to us, however, that if the difference in rotation can be connected with association, it should diminish as the solutions are diluted, since such dilution decreases the degree of association: in fact, experimental results on the dependence of the rotation of N-benzoyl-α-phenylethylamine in benzene and methanol on the concentration [60,61] show an increase in the difference with dilution.

In addition, neither of these points of view can explain the existence of two crystalline forms.

We are now carrying out a spectropolarimetric study of the behavior of amides and of compounds known to be tautomeric – derivatives of acetoacetic and aminocrotonic esters.

EXPERIMENTAL PART

The measurement of the optical activity was carried out with the spectropolarimeter described in a preceeding communication [2]. In the visible and near ultraviolet region of the spectrum, tubes 1-2 dm long, and in the region below 340-320 mμ, tubes 0.1 and 0.05 dm long were used for measuring the absorption. The solutions for measurement were prepared by dissolving a sample (0.1-0.4 g) in a calibrated 10-ml measuring flask.

The results of the spectropolarimetric measurements are given in Figs. 1 and 2 and in Tables 1 and 2. We carried out measurements at shorter wavelength than those shown in the tables; however, in view of the fact that, for the reason given in the preceeding communication [2], the results in this region are less reliable and have no importance for the question under consideration, these results are not included in the Tables: the last figure cited for each substance corresponds to the wavelength at which we observed a maximum in the rotatory dispersion curve.

N-benzoyl-α-phenylethylamine (I) was obtained from (-)-α-phenylethylamine by Schotten – Bauman benzoylation. The product, recrystallized twice from methanol and then from pentane, had m.p. 128-129°

Found %: N 6.26. $C_{15}H_{15}ON$. Calculated %: N 6.22.

After boiling this for 1 hour with 70% CH_3OH, crystals with m.p. 123-124° precipitated, the analytical results for which agreed with the previous ones. The crystals melting at 123-124°, on slowly increasing the temperature solidified again and remelted at 128-129°. A mixed sample of the two forms, ground in a mortar, melted at 128-129°; in a mixed sample prepared by dissolving the two forms in ether, part of the material melted at 122.5° and the main mass at 127.5-128.5°

N-benzyl-α-phenylethylamine (IV) was obtained from (-)-α-phenylethylamine and benzyl chloride as described in the literature [67]. Its benzoyl derivative (II) was obtained by the Schotten – Bauman method; on recrystallization from dilute methanol, and oil separated which slowly solidified. M.p. 68-70°

Found %: N 4.97. $C_{22}H_{21}ON$. Calculated %: N 4.44.

TABLE 1. Molecular Rotation of the Benzoyl derivative of (-)-α-phenylethylamine

λ in mμ	Solvent and concentration (in parentheses)								
	benzene (1.03)	methanol (1.13)	pyridine		acetic acid		acetone (1.09)	dioxane	
			anhydrous* (1.22)	50% (1.09)	anhydrous* (0.61)	60% (1.42)		anhydrous* (1.05)	50% (0.52)
650	—106°	+11.2°	—9.7°	—	—	—	+71.4°	—26.4°	+10.6°
589	—118	+13.3	0	—	—36°	—	+80.7	—31.5	+18.5
578	—122	+14.6	0	40.2°	—31	+4.3°	+83.2	—31.8	—
546	—140	+16.6	—1.9	47.0	—36	+2.4	+95.0	—36.2	+28.6
493	—181	+26.9	—4.5	—	—45	—	+125	—49.7	—
461	—218	+31.5	—10	—	—54	—	+149	—56.3	—
436	—256	+41.1	—16	114	—61	+15	+174	—67.4	+74.8
405	—317	+58.6	—19	158	—70	+23	+220	—83.5	+108
385	—373	+79.2	—29	—	—75	—	+263	—96.2	—
365	—444	+102	—37	309	—81	+69	+298	—116	+207
349	—518	+136	—44	—	—79	—	+342	—132	—
334	—617	+189	—67	610	—69	+152	+422	—156	+349
324	—	—	—90	—	—	—	+480	—	—
320	—	—	—	—	—	—	+352	—	—
315	—787	+297	—	—	+22	—	+218	—	—
313	—847	+333	—111	—	—	+303	+236	—207	—
309	—834	—	—158	—	—	—	—	—	—
307	—860	+375	—	—	—	—	—	—	—
302	—1000	+458	—	—	+61	—	—	—211	—
297	—1130	+585	—	—	+113	+590	—	—230	—
289	—1360	+837	—	—	—	—	—	—254	—
283	—	+1650	—	—	—	—	—	—	—
280	—	—	—	—	—	—	—	—102	—

* When about 5 drops of water were added to the solution contained in the polarimetric tube (volume about 2 ml), the levo-rotation changed into a dextro-rotation: $[M]_{546}$ + 10°; $[M]_{365}$ + 20°; $[M]_{334}$, + 37°.

N-benzal-α-phenylethylamine (V) was obtained from (-)-α-phenylethylamine and benzaldehyde (see [68]), b.p. 174-175° (13 mm); yield 65%.

N-ethyl-α-phenylethylamine. To a solution of 6.4 ml of (-)-α-phenylethylamine in 20 ml of CH_3OH, 3 ml of acetaldehyde was added. After the mixture had stood for 12 hours, 1.5 g of sodium borohydride was added in portions with mechanical stirring. After 24 hours, the reaction mixture was decomposed with water, and acidified, the methanol was distilled off, the residue was made alkaline and the amine distilled off with steam and extracted with benzene, dried and distilled. A yield of 3.1 g was obtained.

B.p. 78-80° (15 mm), d_4^{20} 0.8956, n_D^{20} 1.5090; MR_D 49.76; calc. 48.38.
Found %: N 9.65, $C_{10}H_{15}N$. Calculated %: N 9.41.

TABLE 2. Molecular Rotation of Derivatives of (-)-α-phenylethylamine in Methyl Alcohol and in Benzene (concentrations given in parentheses)

λ in mμ	α-phenylethylamine		N-benzal-α-phenylethylamine (V)		N-benzyl-α-phenylethylamine (IV)		N-benzoyl-N-benzyl-α-phenylethylamine (II)		N-ethyl-α-phenylethylamine			N-benzoyl-N-ethyl-α-phenylethylamine (III)	
	CH_3OH (2.00)	C_6H_6 (2.41)	CH_3OH (1.16)	C_6H_6 (1.16)	CH_3OH (3.04)	C_6H_6 (3.09)	CH_3OH (0.61)	C_6H_6 (0.63)	without solvent	CH_3OH (3.64)	C_6H_6 (2.50)	CH_3OH (1.35)	C_6H_6 (1.73)
650	−30.3°	−37.9°	+112°	+147°	−99°	−75°	−337°	−367°	−68.8°	−64.8°	−74.3°	−236°	−283°
589	−31.9	−47.9	+125	+162	−121	−91.5	−360	−418	−82.1	−55.4	−82.6	−265	−307
578	−31.7	−48.2	+131	+168	−125	−94.5	−363	−437	−85.5	−64.8	−84.3	−272	−318
546	−36.6	−54.4	+155	+196	−142	−106	−423	−514	−96.6	−75.6	−95.0	−312	−367
493	−47.3	−69.8	+216	+264	−184	−132	−578	−687	—	−97.1	−121	−412	−484
461	−57.2	−82.2	+276	+331	−218	−155	−714	−859	—	−115	−141	−497	−590
436	−64.9	−89.5	+339	+40[illegible]	−250	−187	−850	−1037	−164	−133	−161	−583	−696
405	−80.8	−111	+462	+529	−307	−205	−1100	−1337	−197	−161	−204	−661	−886
385	−94.0	—	+578	+656	−352	−227	−1310	−1467	—	−186	−218	−865	−1054
365	−108	−142	+742	+[illegible]2	−398	−259	−1615	−1994	−255	−216	−246	−1040	−1280
349	−120	—	+885	+[illegible]24	−468	−285	−1930	—	—	—	—	−1300	−1510
334	−139	−175	+1270	+1120	−540	−314	−2350	−3000	−322	−280	−307	−1466	−1835
315	—	—	+1790	+1380	−665	−364	−3260	—	—	—	—	—	—
313	−172	−200	+1840	+1395	−690	—	—	−4340	−377	−340	−363	−1925	−2550
310	—	—	+1920	+1440	—	—	—	—	—	—	—	—	—
309	—	—	+1900	+1310	−708	−376	—	—	—	—	—	—	—
305	—	—	+1360	+1070	−742	—	—	—	−401	—	—	−2200	−2830
302	−191	−224	+977	+1520	−777	−400	−4030	−5570	−406	−390	−407	−2350	−2950
297	—	—	—	—	—	−422	−4470	−6190	—	−392	—	—	—
294	—	—	—	—	—	−432	—	—	—	—	—	—	—
289	—	—	—	—	—	—	—	—	—	−448	—	—	—

Benzoylation by the Schotten – Bauman method gave a viscous oil which did not crystallize (III); it was purified by vacuum distillation. B.p. 191-194° (3 mm).

Found %: N 4.97. $C_{17}H_{19}ON$. Calculated %: N 5.53.

SUMMARY

Spectropolarimetric results and the existence of two forms differing in melting point confirm the existence of amide-iminol tautomerism in the benzoyl derivative of optically active α-phenylethylamine.

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SYNTHESES BASED ON SCLAREOLE

V. PREPARATION OF N,N-DI-(2-CHLOROETHYL)-15-AMINO-$\Delta^{8(20),\ 13(14)}$-SCLARODIENE

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In recent years, the chloroethylamines have found use in medicine as substances showing some inhibitory action on the growth of malignant tumors [1]. Derivatives of tri-(2-chloroethyl)amine (nitrogen mustard) in which, in order to reduce the toxicity, the third chloroethyl group has been substituted by various radicals, have proved valuable. Chloroethylamines of the aliphatic, aromatic, and heterocyclic series have been described [2-4]. The more active of these have been found to be those in which this radical is a natural aminoacid radical [5] or a heterocyclic-radical entering into the composition of biologically important compounds. However, it is considered that certain other natural compounds may also be of interest. Hence, fragments of vitamin A (derivatives of β-ionone) [6], and of steroids [7], have been tested as the third radical.

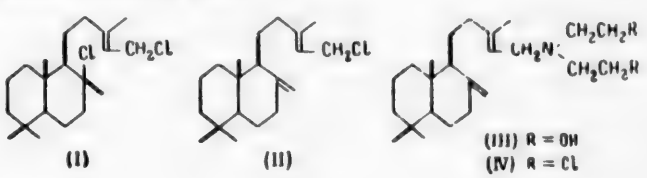
We have synthesized a derivative of chloroethylamine, containing the sclarodiene radical. This appears desirable to us, since the influence of such radicals on the properties of the chloroethylamines has not yet been studied at all.

As starting material for the synthesis we took 8,15-dichloro-$\Delta^{13(14)}$-sclarene (I) and 15-chloro-$\Delta^{8(20),\ 13(14)}$-sclarodiene (II), which are obtained from the diterpene sclareole by hydrochlorination [8] and are very readily obtainable.

The condensation of the dichloride (I) or the monochloride (II) with diethanolamine yielded N,N-di-(2-hydroxyethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene (III). As a result of the condensation of the dihalide (I) with diethanolamine, as in the case of other amines [9], the tertiary chlorine atom at C_8 is readily split out with the formation of a double bond.

The reaction of the base (III) with thionyl chloride yielded N,N-di-(2-chloroethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene (IV) in the form of its hydrochloride. Compounds (III) and (IV), and their derivatives, have not been described in the literature.

Comparative tests with sarcolysine showed that the substance (IV) possesses practically no activity towards the sarcoma-45 of rats and Ehrlich's cancer of mice.



(I) (II) (III) R = OH (IV) R = Cl

EXPERIMENTAL PART

Hydrochloride of N,N-di-(2-hydroxyethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene. A mixture of 690 mg of the dichloride (I), 840 mg of diethanolamine, and 14 ml of alcohol was heated on the water bath for 1 hour. The mixture was allowed to stand for 18 hours. Then the solvent was distilled off, and the residual oil was extracted with ether (three times). The ethereal solution was washed with water and dried with sodium sulphate, and the ether was distilled off. The residue was dissolved in 5 ml of absolute ether and a current of dry hydrogen chloride was bubbled

through the solution. Thereupon, a yellow viscous oil separated as a precipitate; it began to crystallize after some minutes. The precipitate was separated by filtration, washed with absolute ether, and crystallized twice from a 15 : 1 mixture of ethyl ether and ethanol. A yield of 510 mg of a white crystalline substance in the form of scales with m.p. 106-107° was obtained.

Found %: C 69.56, 69.66; H 10.78, 10.65; N 3.23, 3.24; Cl 8.61, 9.06. $C_{24}H_{45}O_2N \cdot HCl$. Calculated %: C 69.65; H 10.64; N 3.39; Cl 8.58.

N,N-di-(2-hydroxyethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene (III). The substance formed on shaking 250 mg of the hydrochloride with 5 ml of a 10% solution of alkali was extracted twice with ether. After the ethereal extract had been washed with water and dried and the ether had been distilled off, a faintly yellow very viscous liquid with a characteristic smell was obtained. B.p. 182-184° at 0.03 mm, n_D^{20} 1.5152.

Found %: C 76.42, 76.70; H 11.47, 11.59; N 3.66, 3.51. $C_{24}H_{43}O_2N$. Calculated %: C 76.40; H 11.41; N 3.71.

Reaction of 15-chloro-$\Delta^{8(20),\ 13(14)}$-sclarodiene with diethanolamine. A mixture of 1 g of the liquid mixture of monochlorides obtained after separation of the crystalline dichloride (I), 0.7 g of diethanolamine and 5 ml of alcohol was heated under a reflux condenser until the oily residue completely dissolved. Heating was continued for a further 1 hour, and then the mixture was allowed to stand at room temperature for a day. Further treatment was the same as for the hydrochloride of the base (III). A yield of 0.6 g of material was obtained. After crystallization from a mixture of ethyl ether and ethanol, it had m.p. 106-107°. It gave no depression of the melting point with the hydrochloride of the base (III) obtained from the dichloride (I).

Hydrochloride of N,N-di-(2-chloroethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene. A solution was made of 420 mg of the base (III) in 5 ml of dry chloroform and cooled to 0°, and 1 ml of thionyl chloride was added. The mixture was allowed to stand for 15 hours at 10°, after which the solution had become brown. The chloroform and the excess of thionyl chloride were distilled off in vacuo, and the residue was dissolved in benzene and twice heated with activated carbon. After filtration and partial evaporation of the benzene, the solution yielded a flocculent precipitate, which was separated by filtration. The residual solution was evaporated to half its volume, as a result of which a further amount of substance separated. The amount of substance obtained was 350 mg. After two recrystallizations from anhydrous toluene and drying in vacuo, it had m.p. 166-167° (decomposition).

Found %: C 64.10, 64.01; H 9.52, 9.62; N 3.34, 3.20; Cl 23.58, 23.38. $C_{24}H_{41}NCl_2 \cdot HCl$. Calculated %: 63.93; H 9.32; N 3.11; Cl 23.64.

The base (IV) obtained from the hydrochloride, like the base (III), was a yellow liquid with a sharp smell; n_D^{18} 1.5265.

SUMMARY

N,N-di-(2-hydroxyethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene has been obtained by the condensation of 8,15-dichloro-$\Delta^{13(14)}$-sclarene and 15-chloro-$\Delta^{8(20),\ 13(14)}$-sclardiene with diethanolamine and has been converted with thionyl chloride into N,N-di-(2-chloroethyl)-15-amino-$\Delta^{8(20),\ 13(14)}$-sclarodiene.

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THE LIGNANES OF THE JUNIPERS OF THE SOVIET UNION

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Podophyllotoxin and compounds related to it, which belong to the group of lignanes*, have attracted particular attention since the possibility of suppressing the growth of malignant new formations has been observed in experiment with some of them [1]. Although this discovery has not yet found practical application, it has served as a stimulus to the appearance of a series of chemical investigations devoted on the one hand to the determination of the structure of some still unknown compounds and on the other hand to finding new members of this group of substances. The latter is favored by the fact that podophyllotoxin and other biologically active lignanes have been found in some other plants besides duck's foot, particularly in junipers. For the investigation of the junipers, we are obliged mainly to Hartwell and his co-workers, who discovered new compounds of the lignane group in the needles of these plants [2].

An investigation of the junipers distributed in the Soviet Union was carried out by us on the material collected by expeditions from our Institute under the leadership of P. S. Massagetov to Asia Minor and the Caucasus. To extract the lignanes from the juniper needles, we used a method developed by the American workers [3], in some cases introducing supplementary operations into it – for example, a second chromatographic separation from another solvent.

As a rule, we subjected the whole of the materials of the extract to biological assay (by the method of the suppression of spermatogenesis in the rat [4]) after chromatography on alumina of a solution of these materials in anhydrous alcohol; only in one case (Juniperus seravschanica Kom.; sample No. 9) did we not succeed in isolating a crystalline substance of the podophyllotoxin group from the whole of the materials of the extract which possessed biological activity.

We investigated 9 different types of junipers; the results obtained are given in the Table, where the time and place of collection of the plants are also given. It can be seen from the Table that no lignanes could be isolated from five varieties, podophyllotoxin was isolated from three varieties, and silicicolin (desoxypodophyllotoxin) [5] from one type. No other derivatives of podophyllotoxin were found in the plants investigated by us. Thus, the investigation of Russian junipers has shown that they contain the same lignanes as the majority of the junipers investigated by the foreign authors. We found the content of lignanes in the needles to be extremely low (hundredths of 1%).

It is interesting to note that two crystalline substances, optically inactive and having ultraviolet spectra completely different from the lignanes, were isolated incidentally from two types of materials; investigation of these substances is still not completed. In one case (J. sabina L; sample No. 7) one of these substances (I, $C_{12}H_{12}O_4$, m.p. 189°) accompanied podophyllotoxin; in another case, the two substances (I and II, $C_{13}H_{14}O_4$, m.p. 90°) were isolated from a plant (J. polycarpus Koch.; sample No. 6) which did not contain lignanes. We have not found any mention in Hartwell's papers of the isolation of similar substances from juniper needles.

As was to be expected, in working with podophyllotoxin we observed its tendency to polymorphism and to the formation of solvates; these properties are absent in its acetyl derivative and in silicicolin.

EXPERIMENTAL PART

As already mentioned, we used Hartwell's method for the isolation of the lignanes. Here, as an example, will be described the isolation of podophyllotoxin from J. sabina (sample No. 8) and silicicolin from J. foetidissima (sample No. 5).

* According to Hartwell's definition [1], substances the structure of which is based on 2,3-dibenzylbutane must be called lignanes.

Sample No.	Name of plant	Time and place of collection	Biological activity	Lignane	Content (in %)
1	Juniperus turkestanica Kom.	Kirgiz Ala-Tau. August, 1955	–	None	–
2	Juniperus pseudo-sabina Fisch et. Mey	Tyan'-Shan'. September, 1955	+	Podophyllotoxin	0.005
3	Juniperus depressa Stev.	Northern Caucasus. September, 1957	–	None	–
4	Juniperus oxycedrus L.	Northern Caucasus August, 1957	–	None	–
5	Juniperus foetidissima W.	Armenia August, 1957	+	Silicicolin	0.038
6	Juniperus polycarpus Koch.	Northern Caucasus September, 1957	–	None	–
7	Juniperus sabina L.	Northern Caucasus September, 1957	+	Podophyllotoxin	0.052
8	Juniperus sabina L.	Tyan'-Shan'. September, 1948	+	Podophyllotoxin	0.016
9	Juniperus serav-schanica Kom.	Turkestan Range August, 1958	+	None	–

Isolation of podophyllotoxin. Acetone (64 liters in 3 lots) was allowed to percolate through 8 kg of air-dry needles (sample No. 8); after distilling off the acetone, a green resin (421 g, 5.26%) remained which was extracted with several portions of heptane with gentle agitation; the heptane-insoluble residue weighed 227 g (2.83%). It was dissolved in 12 parts of anhydrous alcohol and the solution was passed through a column containing 3 kg of alumina (for chromatography); elution of the materials from the column with anhydrous alcohol was carried on until the eluate (after evaporation) showed the absence of dissolved materials. After the alcohol had been distilled off in vacuo, the residue was treated with ethyl acetate and the part not dissolving was discarded; the ethyl acetate was distilled from the solution in vacuo, the residue was treated with xylene, the solution was filtered and placed in a refrigerator for crystallization, which was carried out for a prolonged time. The crystals which precipitated were separated off on a glass filter, washed with xylene, and dried; the yield was 1.3 g. After several recrystallizations from hot alcohol and drying in vacuo over P_2O_5 (100°, 2 mm) the podophyllotoxin obtained had m.p. 182-184°, $[\alpha]_D^{20}$ -114.2° (c, 1.006; alcohol); -122.2° (c, 1.014; chloroform); -152.2° (c, 1.025; pyridine); elementary analysis of it gave results in conformity with the formula $C_{22}H_{22}O_8$.

Found %: CH_3O 22.4. $C_{22}H_{22}O_8$. Calculated %: CH_3O 22.5.

The substance gave no depression of the melting point in admixture with podophyllotoxin obtained by us from imported podophyllin by Ambrosi's method [6]. The ultraviolet spectra of the two materials agreed with those given in the literature [7]: $\lambda_{max.}$ 292 mμ; log ε, 3.65; $\lambda_{min.}$, 260 mμ; log ε, 3.08 (in alcohol); the infrared spectra also coincided, displaying the presence of absorption bands of the OH group at 3360 cm^{-1} and the CO group of a γ-lactone at 1773 cm^{-1}.

On acetylation of the substance isolated by us with acetic anhydride in pyridine, we obtained an acetyl derivative with m.p. 208.5°, $[\alpha]_D^{20}$ -143.3° (c, 1.11; chloroform), which gave no depression of the melting point in admixture with the product of acetylation of podophyllotoxin from podophyllin.

Isolation of silicicolin. Acetone (42 liters, in 3 portions) was allowed to percolate through 5.38 kg of air-dry needles (sample No. 5); after the solvent had been distilled off, there remained 300 g (5.57%) of a resin from which, after treatment with heptane, 138 g (2.57%) of insoluble materials was obtained. The product insoluble in heptane (138 g) was dissolved in 900 ml of anhydrous alcohol, and the solution was passed through a column containing 1500 g of alumina, which was then washed as described above. The residue, after distillation of the alcohol, weighed 67 g. It was dissolved in 1 liter of xylene, but the solution did not give crystals even after long standing in the refrigerator; therefore, the xylene was distilled off in vacuo completely and the residue was treated with 1 liter of benzene; the solution soon yielded an amorphous precipitate which, after a day, was filtered off (19 g), and the filtrate was

passed through a column with 800 g of alumina which was then washed with benzene. The first two fractions (0.5 and 1.03 liter) were evaporated to dryness in vacuo, and the residue was treated with alcohol, whereupon a crystalline substance with m.p. 84° (0.25 g), not further investigated, separated; after the alcohol had been distilled off, there remained a brown resin (4.7 g) which, after further treatment (similar to that described below for the third fraction), gave no crystalline materials. The third fraction (1550 ml) yielded, after the benzene had been distilled off, 7.6 g of a greenish resin; dissolution of this xylene and keeping the solution in the refrigerator gave no results. The solvent was distilled off, the residue was dissolved in 15 ml of anhydrous alcohol, and the solution was boiled for 1.5 hours with 1 g of activated carbon, filtered and placed in the refrigerator. After the lapse of 35 days, the crystals separating out were filtered off; they weighed 2.04 g and melted at 163-164°. After recrystallization from anhydrous alcohol, they had m.p. 166°; $[\alpha]_D^{20}$, -101.5° (c, 1.04; alcohol); -113.9° (c, 1.01; chloroform); -180° (c, 1.04; pyridine). The results of elementary analysis corresponded to the formula $C_{22}H_{22}O_7$.

Found %: CH_3O 22.95. $C_{22}H_{22}O_7$. Calculated %: CH_3O 23.36.

The ultraviolet spectrum agreed with the spectrum of silicicolin given in the literature [7]; λ_{max} 294 mμ, log ε 3.69; λ_{min} 259 mμ, log ε, 3.07 (in alcohol); in the infrared spectrum, the OH-group absorption band was absent; the absorption band for the CO group of a γ-lactone was just as intense as in the spectrum of podophyllotoxin.

For lack of a sample of silicicolin for a direct comparison, we carried out an experiment on the epimerization of our substance into silicicolin B (desoxypicropodophyllin) [5] for identification purposes: 0.206 g of the substance, 0.04 g of anhydrous sodium acetate, and 3 ml of anhydrous alcohol were boiled under a reflux condenser for 17 hours; after cooling and dilution with water, the precipitate was filtered off dried 0.14 g and recrystallized from anhydrous alcohol; m.p. 172-173°; $[\alpha]_D^{20}$, + 36° (c, 1.08; chloroform); literature data [5]; m.p. 170.7-172°; $[\alpha]_D^{21}$, + 32° (c, 0.5; chloroform).

SUMMARY

The content of lignanes in the needles of 9 varieties of junipers of those distributed in the Soviet Union has been investigated; from the needles of three types, podophyllotoxin has been obtained and from the needles of one type silicicolin (desoxypodophyllotoxin); no lignanes could be isolated from the needles of five varieties.

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LETTER TO THE EDITOR

CORRECTION TO THE PAPER OF N. K. KOCHETKOV, A. M. LIKHOSHERSTOV, AND É. I. BUDOVSKII "PYRROLIZIDINE ALKALOIDS

I. SYNTHESIS OF 1-HYDROXYMETHYLPYRROLIZIDINE (d, *l* -TRACHELANTHAMIDINE)"

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 5,
pp. 1735, May, 1961

In the published paper, (N. K. Kochetkov, A. M. Likhosherstov, and É. I. Budovskii, ZhOKh, 30, 2077, 1960), the authors made an error as the result of a misunderstanding in the figure of the infrared spectra on page 2080. In fact, curve 1 must be taken as the spectrum of natural trachelanthamidine, curve 2 as the spectrum of synthetic hydroxymethylpyrrolizidine, and curve 3 as the spectrum of natural lindelofidine.

N. K. Kochetkov, A. M. Likhosherstov and É. I. Budovskii

DISCUSSION

THE QUESTION OF THE REACTIONS OF α,β-UNSATURATED ACIDS WITH TRIALKYL PHOSPHITES

Gil'm Kamai and V. A. Kukhtin

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In the twelfth issue of "Zhurnal Obshchei Khimii" for 1960, a paper of V. A. Ginsburg and A. Ya. Yukubovich [1] was published on the reaction of esters of acrylic acids with phosphites. The authors of this paper established that, under fairly severe conditions (150° in a sealed tube) acrylates are capable of reacting with trialkyl phosphates with the formation of dialkoxyphosphinyl carboxylic acids. Ginsbrug and Yakubovich put forward the hypothesis that the reactions of trialkyl phosphites with α,β-unsaturated acids studied by us [2-6] possibly proceed by a preliminary esterification of the acid by the phosphite with a subsequent addition of the trialkyl phosphite to the ester of the unsaturated acid.

The reactions of the phosphites and esters of alkylphosphonic acids studied by us [7] with acrylic acids proceed incomparably more vigorously than the reaction of phosphites with esters of these acids. Trialkyl phosphites react extremely vigorously with acrylic acid even at room temperature; in the case of alkylphosphonic acids, the reaction goes so vigorously that cooling is required. In our paper [2], which Ginsburg and Yakubovich do not cite for some reason or other, it was shown that under the conditions of the reaction of acrylic acids with trialkylphosphates the former undergo practically no esterification by the trialkyl phosphites. In our experiments, only a short period of heating was used at the end of the reaction to complete the conversion of the intermediate reaction product (the formation of which we demonstrated experimentally [3,5,6]) into the final product of the Arbuzov rearrangement. It is possible that, on heating in the final stage of the reaction the partial formation of esters of the unsaturated acids takes place; however, under these conditions they are incapable of reacting with trialkyl phosphites. We repeatedly carried out the reaction of triethyl phosphite with methyl methacrylate by prolonged heating at 100-120°. We found that, on heating an equimolecular mixture of triethyl phosphite and methyl methacrylate at 120° for 15 hours in a flask with a reflux condenser, no formation of an ester of β-(diethoxyphosphinyl)-isobutyric acid took place. Only at 140-150°, at an elevated pressure, and in the presence of hydroquinone did the reaction reported by Ginsburg and Yakubovich take place.

We have not studied the possibility of the addition of esters of acids of trivalent phosphorus to the conjugated system C = C − C = O solely on the example of α, β-unsaturated acids; an analogous reaction goes with α,β-unsaturated aldehydes. In the same issue of the journal, a paper of Ginsburg and Yakubovich [8] was published in which they confirmed that phosphites react with acrolein in accordance with the scheme described by us and themselves proposed a heterolytic scheme for the reaction of phosphites with unsaturated aldehydes. Ginsburg and Yakubovich are not only well acquainted with our work, but have reproduced the experiments with acrylic and methacrylic acids. Consequently the fundamental difference in reactivity between acrylic acids and esters of these acids with respect to trialkyl phosphites must be well known to them. In view of what has been stated above, it is incomprehensible why Ginsburg and Yakubovich consider it possible to put forward a hypothesis which is completely baseless and contrary to the experimental facts on the nature of the reaction of phosphites with acrylic acids.

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SIGNIFICANCE OF ABBREVIATIONS MOST FREQUENTLY ENCOUNTERED IN SOVIET PERIODICALS

FIAN	Phys. Inst. Acad. Sci. USSR
GDI	Water Power Inst.
GITI	State Sci.-Tech. Press
GITTL	State Tech. and Theor. Lit. Press
GONTI	State United Sci.-Tech. Press
Gosenergoizdat	State Power Press
Goskhimizdat	State Chem. Press
GOST	All-Union State Standard
GTTI	State Tech. and Theor. Lit. Press
IL	Foreign Lit. Press
ISN (Izd. Sov. Nauk)	Soviet Science Press
Izd. AN SSSR	Acad. Sci. USSR Press
Izd. MGU	Moscow State Univ. Press
LEIIZhT	Leningrad Power Inst. of Railroad Engineering
LET	Leningrad Elec. Engr. School
LETI	Leningrad Electrotechnical Inst.
LETIIZhT	Leningrad Electrical Engineering Research Inst. of Railroad Engr.
Mashgiz	State Sci.-Tech. Press for Machine Construction Lit.
MEP	Ministry of Electrical Industry
MES	Ministry of Electrical Power Plants
MESEP	Ministry of Electrical Power Plants and the Electrical Industry
MGU	Moscow State Univ.
MKhTI	Moscow Inst. Chem. Tech.
MOPI	Moscow Regional Pedagogical Inst.
MSP	Ministry of Industrial Construction
NII ZVUKSZAPIOI	Scientific Research Inst. of Sound Recording
NIKFI	Sci. Inst. of Modern Motion Picture Photography
ONTI	United Sci.- Tech. Press
OTI	Division of Technical Information
OTN	Div. Tech. Sci.
Stroiizdat	Construction Press
TOE	Association of Power Engineers
TsKTI	Central Research Inst. for Boilers and Turbines
TsNIEL	Central Scientific Research Elec. Engr. Lab.
TsNIEL-MES	Central Scientific Research Elec. Engr. Lab.-Ministry of Electric Power Plants
TsVTI	Central Office of Economic Information
UF	Ural Branch
VIESKh	All-Union Inst. of Rural Elec. Power Stations
VNIIM	All-Union Scientific Research Inst. of Metrology
VNIIZhDT	All-Union Scientific Research Inst. of Railroad Engineering
VTI	All-Union Thermotech. Inst.
VZEI	All-Union Power Correspondence Inst.

NOTE: Abbreviations not on this list and not explained in the translation have been transliterated, no further information about their significance being available to us. –Publisher.

Soviet Journals Available in Cover-to-Cover Translation

ABBREVIATION	RUSSIAN TITLE	TITLE OF TRANSLATION	PUBLISHER	TRANSLATION BEGAN Vol.	Issue	Year
AÉ	Atomnaya énergiya	Soviet Journal of Atomic Energy	Consultants Bureau	1	1	1956
Akust. zh.	Akusticheskii zhurnal	Soviet Physics – Acoustics	American Institute of Physics	1	1	1955
	Antibiotiki	Antibiotics	Consultants Bureau	4	1	1959
Astr(on). zh(urn).	Astronomicheskii zhurnal	Soviet Astronomy–AJ	American Institute of Physics	34	1	1957
Avto(mat). svarka	Avtomaticheskaya svarka	Automatic Welding	British Welding Research Association (London)		1	1959
	Avtomatika i Telemekhanika	Automation and Remote Control	Instrument Society of America	27	1	1956
	Biofizika	Biophysics	National Institutes of Health*		1	1957
	Biokhimiya	Biochemistry	Consultants Bureau	21	1	1956
Byull. éksp(erim). biol. i med.	Byulleten' éksperimental'noi biologii i meditsiny	Bulletin of Experimental Biology and Medicine	Consultants Bureau	41	1	1959
DAN (SSSR) / Dokl(ady) AN SSSR	Doklady Akademii Nauk SSSR	The translation of this journal is published in sections, as follows:				
		Doklady Biochemistry Section	American Institute of Biological Sciences	106	1	1956
		Doklady Biological Sciences Sections (Includes: Anatomy, biophysics, cytology, ecology, embryology, endocrinology, evolutionary morphology, genetics, histology, hydrobiology microbiology, morphology, parasitology, physiology, zoology sections)	American Institute of Biological Sciences	112	1	1957
Life Sciences		Doklady Botanical Sciences Sections (Includes: Botany, phytopathology, plant anatomy, plant ecology, plant embryology, plant physiology, plant morphology sections)	American Institute of Biological Sciences	112	1	1957
		Proceedings of the Academy of Sciences of the USSR, Section: Chemical Technology	Consultants Bureau	106	1	1956
Chemical Sciences		Proceedings of the Academy of Sciences of the USSR, Section: Chemistry	Consultants Bureau	106	1	1956
		Proceedings of the Academy of Sciences of the USSR, Section: Physical Chemistry	Consultants Bureau	112	1	1957
		Doklady Earth Sciences Sections (Includes: Geochemistry, geology, geophysics, hydrogeology, mineralogy, paleontology, petrography, permafrost sections)	American Geological Institute	124	1	1959
Earth Sciences		Proceedings of the Academy of Sciences of the USSR, Section: Geochemistry	Consultants Bureau	106-123	1-6	1957-1958
		Proceedings of the Academy of Sciences of the USSR, Sections: Geology	Consultants Bureau	106-123	1-6	1957-1958
Mathematics		Doklady Soviet Mathematics	The American Mathematics Society	131	1	1961
		Soviet Physics–Doklady (Includes: Aerodynamics, astronomy, crystallography, cybernetics and control theory, electrical engineering, energetics, fluid mechanics, heat engineering, hydraulics, mathematical physics, mechanics, physics, technical physics, theory of elasticity sections)	American Institute of Physics	106	1	1956
Physics		Proceedings of the Academy of Sciences of the USSR, Applied Physics Sections (does not include mathematical physics or physics sections)	Consultants Bureau	106-117	1	1956-1957
Derevoobrabat. prom-st'.	Derevoobrabatyvayushchaya promyshlennost'	Wood Processing Industry	Timber Development Association (London)		9	1959
	Élecktrosvyaz	Telecommunications	Massachusetts Institute of Technology*		1	1957
Éntom(ol). oboz(renie)	Éntomologicheskoe obozrenie	Entomological Review	American Institute of Biological Sciences	38	1	1959
Farmakol. (i) toksikol(ogiya)	Farmakologiya i toksikologiya	Pharmacology and Toxicology	Consultants Bureau	20	1	1957
FMM	Fizika metallov i metallovedenie	Physics of Metals and Metallography	Acta Metallurgica*	5	1	1957
Fiziol. zhurn. SSSR (im. Sechenova)	Fiziologicheskii zhurnal im. I. M. Sechenova	Sechenov Physiological Journal USSR	National Institutes of Health*		1	1957
Fiziol(ogiya) rast.	Fiziologiya rastenii	Plant Physiology	American Institute of Biological Sciences	4	1	1957
	Geokhimiya	Geochemistry	The Geochemical Society		1	1958
FTT	Fizika tverdogo tela	Soviet Physics–Solid State	American Institute of Physics	1	1	1959
Izmerit. tekh(nika)	Izmeritel'naya tekhnika	Measurement Techniques	Instrument Society of America		1	1959
Izv. AN SSSR, O(td). Kh(im). N(auk)	Izvestiya Akademii Nauk SSSR: Otdelenie khimicheskikh nauk	Bulletin of the Academy of Sciences of the USSR: Division of Chemical Sciences	Consultants Bureau		1	1952

continued

Izv. AN SSSR, O(td). T(ekhn). N(auk): Met(all). i top.	(see Met. i top.)				
Izv. AN SSSR Ser. fiz(ich).	Izvestiya Akademii Nauk SSSR: Seriya fizicheskaya	Bulletin of the Academy of Sciences of the USSR: Physical Series	Columbia Technical Translations	1	1954
Izv. AN SSSR Ser. geofiz.	Izvestiya Akademii Nauk SSSR: Seriya geofizicheskaya	Bulletin (Izvestiya) of the Academy of Sciences USSR: Geophysics Series	American Geophysical Union	1	1954
Izv. AN SSSR Ser. geol.	Izvestiya Akademii Nauk SSSR: Seriya geologicheskaya	Izvestiya of the Academy of Sciences of the USSR: Geologic Series	American Geological Institute	1	1958
Kauch. i rez.	Kauchuk i rezina	Soviet Rubber Technology	Research Association of British Rubber Manufacturers 18	1	1959
	Kinetika i kataliz	Kinetics and Catalysis	Consultants Bureau 1	3	1960
	Koks i khimiya	Coke and Chemistry USSR	Coal Tar Research Association (Leeds, England)	1	1958
Kolloidn. zh(urn).	Kolloidnyi zhurnal	Colloid Journal	Consultants Bureau 14	1	1952
	Kristallografiya	Soviet Physics – Crystallography	American Institute of Physics 2	1	1957
Metalov. i term. obrabot. metal.	Metallovedenie i termicheskaya obrabotka metallov	Metal Science and Heat Treatment of Metals	Acta Metallurgica 6	1	1958
	Metallurg	Metallurgist	Acta Metallurgica	1	1957
Met. i top.	Metallurgiya i topliva	Russian Metallurgy and Fuels	Eagle Technical Publications	1	1960
Mikrobiol.	Mikrobiologiya	Microbiology	American Institute of Biological Sciences 26	1	1957
OS	Optika i spektroskopiya	Optics and Spectroscopy	American Institute of Physics	6	1959
	Pochvovedenie	Soviet Soil Science	American Institute of Biological Sciences	1	1958
	Priborostroenie	Instrument Construction	British Scientific Instrument Research Association	1	1959
Pribory i tekhn. éks(perimenta)	Pribory i tekhnika éksperimenta	Instruments and Experimental Techniques	Instrument Society of America	1	1957
Prikl. matem. i mekh.	Prikladnaya matematika i mekhanika	Applied Mathematics and Mechanics	American Society of Mechanical Engineers	1	1958
PTÉ	(see Pribory i tekhn. éks.)				
	Problemy Severa	Problems of the North	National Research Council of Canada		
Radiotekh.	Radiotekhnika	Radio Engineering	Massachusetts Institute of Technology* 12	1	1957
Radiotekh. i élektronika	Radiotekhnika i élektronika	Radio Engineering and Electronics	Massachusetts Institute of Technology* 2	1	1957
	Stanki i instrument	Machines and Tooling	Production Engineering Research Assoc.	1	1959
	Stal'	Stal (In English)	Iron and Steel Institute	1	1959
Stek. i keram.	Steklo i keramika	Glass and Ceramics	Consultants Bureau 13	1	1956
Svaroch. proiz-vo	Svarochnoe proizvodstvo	Welding Production	British Welding Research Association	4	1959
Teor. veroyat. i prim.	Teoriya veroyatnostei i ee primenenie	Theory of Probability and Its Applications	Society for Industrial and Applied Mathematics	1	1956
Tsvet. Metally	Tsvetnye metally	Nonferrous Metals	Primary Sources	1	1960
UFN	Uspekhi fizicheskikh Nauk	Soviet Physics – Uspekhi (partial translation)	American Institute of Physics 66	1	1958
UKh	Uspekhi khimii	Russian Chemical Reviews	The Chemical Society (London)	1	1960
UMN	Uspekhi matematicheskikh nauk	Russian Mathematical Surveys	London Mathematical Society 15	1	1960
Usp. fiz. nauk	(see UFN)				
Usp. khim(ii)	(see UKh)				
Usp. matem. nauk	(see UMN)				
Usp. sovr. biol.	Uspekhi sovremennoi biologii	Russian Review of Biology	Oliver and Boyd	48	1959
Vest. mashinostroeniya	Vestnik mashinostroeniya	Russian Engineering Journal	Production Engineering Research Assoc.	4	1959
Vop. gem. i per. krovi	Voprosy gematologii i perelivaniya krovi	Problems of Hematology and Blood Transfusion	National Institutes of Health*	1	1957
Vop. onk.	Voprosy onkologii	Problems of Oncology	National Institutes of Health*	1	1957
Vop. virusol.	Voprosy virusologii	Problems of Virology	National Institutes of Health*	1	1957
Zav(odsk). lab(oratoriya)	Zavodskaya laboratoriya	Industrial Laboratory	Instrument Society of America 25	1	1959
ZhAKh Zh. anal(it). khimii	Zhurnal analiticheskoi khimii	Journal of Analytical Chemistry USSR	Consultants Bureau 7	1	1952
ZhETF Zh. éksperim. i teor. fiz.	Zhurnal éksperimental'noi i theoreticheskoi fiziki	Soviet Physics–JETP	American Institute of Physics 28	1	1955
ZhFKh Zh. fiz. khimii	Zhurnal fizicheskoi khimii	Russian Journal of Physical Chemistry	The Chemical Society (London)	7	1959
ZhMÉI Zh(urn). mikrobiol. épidemiol. i immunobiol.	Zhurnal mikrobiologii, épidemiologii i immunobiologii	Journal of Microbiology, Epidemiology and Immunobiology	National Institutes of Health*	1	1957
ZhNKh Zh(urn). neorgan(ich). khim(ii)	Zhurnal neorganicheskoi khimii	The Russian Journal of Inorganic Chemistry	The Chemical Society (London)	1	1959
ZhOKh Zh(urn). obshch(ei) khimii	Zhurnal obshchei khimii	Journal of General Chemistry USSR	Consultants Bureau 19	1	1949
ZhPKh Zh(urn). prikl. khimii	Zhurnal prikladnoi khimli	Journal of Applied Chemistry USSR	Consultants Bureau 23	1	1950
ZhSKh Zh(urn). strukt. khimii	Zhurnal strukturnoi khimii	Journal of Structural Chemistry	Consultants Bureau 1	1	1960
ZhTF Zh(urn). tekhn. fiz.	Zhurnal teknicheskoi fiziki	Soviet Physics–Technical Physics	American Institute of Physics 26	1	1956
Zh(urn). vyssh. nervn. deyat. (im. Pavlova)	Zhurnal vysshei nervnoi deyatel'nosti (im. I. P. Pavlova)	Pavlov Journal of Higher Nervous Activity	National Institutes of Health*	1	1958

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